

The Impact of Fever and its Treatment in Critically Ill Children

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Thesis submitted in fulfilment of the requirements for the
degree of PhD

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Declaration of Content

I, Samiran Ray, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Acknowledgements

I would like to thank all the patients and staff on the intensive care units at Great Ormond Street Hospital for their support.

I am also grateful to the following people for their very useful advice along the way: Professors David Harrison, Frank Harrell and Christina Pagel; Dr Nazima Pathan and Dr Rosan Meyer; all my co-authors in my publications, especially Ms Libby Rogers, Dr Katharine Brown, Dr Padmanabhan Ramnarayan and Dr Simon Eaton. I am very grateful to ICNARC for allowing me to be part of the Fever Feasibility Study.

I would like to thank the amazing Critical Care Research Team at Great Ormond Street Hospital, especially Luran, Amy, Eugenia, Fran, Holly and Gareth. I thank Dr Sainath Raman for helping me believe this was possible and for his useful suggestions throughout.

I thank Professor Nigel Klein for his support and guidance as a second supervisor and wish him well in the difficult months ahead.

None of this work would have been possible without the exceptional support and guidance from Professor Mark Peters. Thank you.

And to my wife, Shona - thank you for being patient over hundreds of lost evenings and weekends. I *will* paint the garden chairs some day.

Abstract

Background: Fever is associated with improved mortality in critically ill adults with infection. Although infection is common in critically ill children, fever is treated, often with the aim to reduce oxygen consumption or improve oxygen delivery. This work tests the hypothesis that in critically ill children, fever impacts on outcomes by significantly imbalancing oxygen consumption and delivery.

Methods: (i) A retrospective study of fever epidemiology in an unselected population of children admitted to the paediatric intensive care unit (PICU); (ii) A prospective study of fever epidemiology in children admitted to PICU with infection; (iii) A prospective study of the use of anti-pyretic interventions in children with infection and fever; (iv) A retrospective study exploring the effectiveness of paracetamol in reducing temperature; (v) A prospective study using indirect calorimetry to measure the changes in oxygen consumption with fever; (vi) Retrospective studies using high-resolution data and pulse-contour analysis to explore haemodynamic changes in children with fever and paracetamol; (vii) An observational study of the association between temperature and mortality in children admitted to PICU and children recruited to the FEAST study in sub-Saharan Africa.

Results: (i) Fever occurred in 4066/10379 (40.1%) children in the first 48-hours of PICU admission. (ii) Seventy-seven of 140 children admitted with infection (55.0%) had a fever within the first 5-days of admission. (iii) 101/140 (72.1%) children were treated with anti-pyretic interventions, with paracetamol used in 99/101 (98.0%). The use of anti-pyretic interventions was correlated with temperature. (iv) Paracetamol was associated with a temperature decrease by 0.78°C (95% CI 0.74-0.82°C) in febrile children following the analysis of 4849 doses. (v) Changes in oxygen consumption with fever were variable, although the data could not be interpreted due to small numbers. (vi) A 1°C rise in temperature was associated with an 8.31/min (95% CI 8.30-8.33) rise in heart rate following an analysis of 7,39,466 data pairs from 170 children; and a 0.11 mmHg (95% CI 0.09-0.12)

rise in mean arterial pressure following analysis of 5,212,439 pairs from 123 children. Rise in temperature was associated with a rise in the cardiac index but fall in the systemic vascular resistance. Paracetamol was associated with a drop in mean blood pressure by 3.02 mmHg (95% CI 1.56-4.47) following multi-variable analysis of 148 doses in 31 children. (vii) Maximum temperature in the first 24-hours of admission had a U-shaped relationship with mortality in 10125 PICU patients. The optimum temperature for survival was 38°C in those with unplanned admissions. Fever was similarly associated with improved survival in children with infection in sub-Saharan Africa without ICU provision.

Conclusions: Fever is common in critically ill children. It is associated with near-equal increases in oxygen delivery and consumption. Given this, it is unlikely that an imbalance between oxygen consumption and delivery impacts on outcomes; fever was associated with a lower mortality compared to those with a maximum temperature of 36.5°C or below.

Impact Statement

Treatments used in ICUs are often aimed at normalising abnormal physiology. However, many of these interventions to normalise physiology, such as blood transfusions, fluid, oxygen and vasoconstrictors have shown little impact on overall recovery. Controlling temperature during fever can reduce the amount of blood pressure support needed and the amount of energy consumed. Yet fever is part of the body's immune response. In critically ill adults with infection fever is associated with improved survival.

Nearly 20000 children are admitted to intensive care units (ICUs) each year in the UK. Fever is common in childhood, and often treated, despite little evidence to support this. Very few studies have explored the impact of fever and its treatment in critically ill children. In these children an increase in temperature may have detrimental effects on oxygen consumption and delivery, the imbalance of which typically characterises critical illness states.

To evaluate the effect of fever treatment in children admitted to ICU, a randomised controlled trial is needed, comparing children who are treated for fever with those who are not. In this thesis, I test many of the assumptions needed to design, conduct and interpret such a trial.

In the largest paediatric ICU (PICU) in the UK, fever occurred in just under 40% children, with most instances occurring early. In those with infection, this rose to 55%. Most of these children were treated with paracetamol, although paracetamol was used in 70% of children regardless of fever. Any trial comparing treatment of fever would need to randomise children early to achieve treatment separation. In children with fever, paracetamol was associated with a fall in temperature by 0.78°C. Regardless, fever often resolved in children who did not receive paracetamol. Temperature separation between trial arms treated with paracetamol or not would be modest. Although ubiquitously used and cheap, the use of paracetamol can be reduced.

The effect of fever on oxygen consumption was difficult to determine. The limited results were consistent with previously described findings in adults, where fever increased oxygen consumption. Fever was associated with an increase in heart rate and cardiac output on average in critically ill children, although there is great variability in this association. Paracetamol however reduced blood pressure. In children who may be haemodynamically unstable needing support on ICU, fever could, therefore, justifiably be left untreated or treated through alternative methods (e.g. surface cooling).

Fever was not associated with increased mortality: on the contrary, a fever was associated with a lower risk of mortality after an unplanned admission. Furthermore, children with fever did not show a different response to increasing oxygen delivery using fluid boluses compared to those without a fever following a retrospective analysis of data from the FEAST trial.

None of these findings preclude the conduct of a trial to assess the treatment of fever in PICU. There are no strong arguments to treat fever with paracetamol to improve oxygen delivery although prevention of fever may reduce oxygen consumption. Whether this brings overall benefit to children on PICU requires a trial, which this thesis supports.

Work published from this thesis (copies included at the end):

Ray S, Rogers L, Brown KL, Peters MJ. The Effect of Acetaminophen on Temperature in Critically Ill Children: A Retrospective Analysis of Over 50,000 Doses. *Pediatr Crit Care Med*. 2018 Mar;19(3):204-209.

Ray S, Brick T, Raman S, Birrell PJ, Klein NJ, Peters MJ. Haemodynamic changes with paracetamol in critically-ill children. *J Crit Care*. 2017 Aug;40:108-112.

Work presented from this thesis:

The relationship between temperature and heart rate in critically ill children: an analysis of 7393328 HR measurements. Oral presentation at the European Society of Paediatric and Neonatal Intensive Care Congress, Salzburg June 2019

Work supported by, although not directly part of this thesis:

Peters MJ, Woolfall K, Khan I, Deja E, Mouncey PR, Wulff J, Mason A, Agbeko RS, Draper ES, Fenn B, Gould DW, Koelewyn A, Klein N, Mackerness C, Martin S, O'Neill L, Ray S, Ramnarayan P, Tibby S, Thorburn K, Tume L, Watkins J, Wellman P, Harrison DA, Rowan KM; FEVER Investigators on behalf of the Paediatric Intensive Care Society Study Group (PICS-SG). Permissive versus restrictive temperature thresholds in critically ill children with fever and infection: a multicentre randomized clinical pilot trial. *Crit Care*. 2019 Mar 7;23(1):69.

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Preface

In 323 BC, aged 32, Alexander the Great was struck by a febrile illness. On the third day of his illness he took a cold bath. Despite feeling better, his fever returned. His physicians recommended further cold baths and chest compresses. On the 12th day he succumbed to his illness and died [Oldach 1998].

This account encapsulates a medical uncertainty that has survived over 2000 years. Fever was associated as a symptom of disease. It was treated and provided symptomatic relief, yet Alexander's disease proved fatal.

Today we know that fever is part of the immune response: the body's protection against disease. This has evolved over hundreds of millions of years, giving animals a survival advantage in overcoming infection. In vitro and animal studies suggest that fever is not a by-product of immune activation, but a potentiator of it.

Did the cold baths help Alexander, or did they contribute to his demise? If fever is part of the armoury in fighting infection, why treat it? Treatment of fever persists today – cold baths have been replaced by paracetamol and aspirin. In 2019, Alexander's possible typhoid fever could have been treated and cured with antibiotics. Does fever matter anymore? Not all infections have cures. Despite antibiotics, some infections prevail. When life is threatened, ordinarily redundant mechanisms such as fever could have a role to play against disease.

The role of fever and its treatment in the intensive care unit (ICU) has been repeatedly questioned by clinicians. Here patients have life threatening illnesses. Fever may provide an advantage in bringing about the resolution of disease. Against this is the argument that the energy needed to generate a fever is ill-afforded in these patients. Fever is widely treated, although whether this is worth doing remains incompletely answered.

Febrile illnesses are the second most common reason for children to present to healthcare professionals (after breathing difficulties) [Armon 2001]. Paracetamol remains the most frequently used over-the-counter treatment in children, despite the National Institute of Health and Clinical Excellence asserting that no outcome benefit for treating fever has ever been demonstrated. The arguments for and against treating fever in adult ICUs can extend to critically ill children. Uncertainty is greater due to paucity of evidence, and differences in immune, haemodynamic and thermoregulatory mechanisms between children and adults.

The central questions that motivated this thesis can be crystallised to two: is fever beneficial or harmful in critically ill children, and should fever be treated in the paediatric ICUs? If fever is beneficial by aiding recovery from illness, then treatment of fever may hinder this. If fever is harmful by worsening shock states for example, then effective treatment of fever may prevent this. Whilst these questions, particularly the latter, need to ultimately be answered through a randomised controlled trial, key information is missing to design, conduct and interpret such a trial appropriately. Critical illness is largely characterised by the imbalance between oxygen consumption and delivery, either at the level of an organ system or the individual. I will focus the questions further: does fever have an impact on the outcome of critically ill children through the effects on oxygen consumption and delivery? In addition, does the treatment of fever reverse this?

In the first chapter, I will explore what is known about fever and its treatment through history and evolution, to glean knowledge about the importance of fever in disease and the immune response. I will discuss the mechanisms behind the generation of fever, as a form of altered thermoregulation. I will detail what is known about the effect of fever and its treatment on oxygen delivery and consumption. Finally, I will address the existing evidence that can guide the management of fever in clinical practice, both in critically ill adults and children.

In the second chapter, I will examine the epidemiology of fever in the paediatric ICU, using both retrospective and prospective methods.

In the third chapter I will describe the use of anti-pyretic treatments using prospective data, and the effect that these have on temperature using retrospective data from a large cohort of unselected ICU patients.

Physiologically, and in the ICU, oxygen delivery is manipulated to match oxygen consumption. In the fourth chapter, I will attempt to measure the effect that fever has on oxygen consumption in critically ill children.

In the fifth chapter, I explore the effects of fever and its treatment on oxygen delivery. Assuming that fever is unlikely to influence haemoglobin concentration, I will concentrate on the determinants of cardiac output: heart rate and stroke volume. Also recognising that blood pressure is measured and often a target to guide treatment in the ICU, I will extend the analysis to examine the effects of fever on blood pressure and vascular resistance.

Finally, In the Chapter 6, I will assess how fever is associated with mortality in critically ill children. In addition to children admitted to ICUs in the UK, I will test this association in a cohort of children from sub-Saharan Africa who had life-threatening infections, but not ICU provision. I compare the two cohorts to try to dissociate the effects of ICU interventions on the effect of fever on mortality. I will also explore whether the presence of fever had an effect on the association between fluid and mortality in the FEAST cohort.

Through this work I will attempt to answer the question whether fever does affect oxygen delivery and consumption, and whether this has an effect on the outcomes of critical illness. Along with this, I will try to find an argument to treat fever (or not) in children admitted to paediatric ICU.

Chapter 1: Introduction

Throughout the history of medicine, the role of fever as friend or foe in disease has remained uncertain. Proponents and opponents of the hypothesis that fever can be protective have come and gone. Accordingly, fever has both been treated as a symptom of disease and induced for treatment of disease. In this introduction, I start by describing the changing theories of fever over time, to help understand modern medicine's attitude towards both. I then assess the scientific knowledge regarding the role of fever in the immune response, through comparative biology and in vitro models. I explore the thermoregulatory mechanisms that permit fever to occur, before concentrating on the epidemiology of fever in the ICU. The question I pose is whether fever affects oxygen consumption and delivery in critically ill children. Therefore, I will describe what is known about the effect of fever on oxygen consumption and delivery. Recent clinical studies have assessed the impact of fever and its treatment on wider clinical outcomes such as mortality: I review these, leading to a series of questions which remain unanswered for children who are critically ill. Finally, I set up the hypothesis that I will try and address in the remainder of this thesis.

1.1 A historical perspective

1.1.1 A brief history of fever: Throughout the history of human civilisation fever has been identified as a feature of illness. Akkadian cuneiform inscriptions from the Mesopotamian civilisation dating back to the 6th century BC used a flaming brazier to depict fever in illness. Hippocrates described in detail changes in body temperature associated with diseases subsequently recognisable as pneumonia, malaria and enteric fever, long before the invention of the thermometer. The Ancient Greeks explained this using the doctrine of the four humours: fever was caused by an excess of yellow bile, associated with the element of fire [Atkins 1982; Thompson 2005].

Following William Harvey's description of the circulation in the 17th century, the humoral theory of fever needed rethinking. Two schools of thought emerged: the iatro-physicists, who believed fever was a product of physical forces such as friction from blood coursing through the circulatory system in fever, and the iatro-chemists, who believed that fever was a product of fermentation and putrefaction [Pehrsson 1964; Mackowiak 1987].

In the early 18th century, Broussais and others correlated post-mortem tissue damage to fever characteristics. Sources of inflammation were felt to be causative of fever, heralding the subsequent discovery of microbial pathogens [Rolleston 1939]. William Welch extended this theory of fever through post-mortem examination of rabbits subjected to hyperthermia, and those who suffered fever due to infection. He also proposed that the fever was produced by a 'ferment' produced by the host leucocytes, in response to both infectious and non-infectious illness. This was the beginning of the cytokine theory of fever [Welch 1888 L3].

In 1875 von Liebermeister postulated that fever results from a disorder that sets the body temperature at a higher level. Welch proposed an area close to the thalamus was involved in the regulation of body temperature in both health and disease, based on temperature changes seen in animal experiments following injury to this area [Welch 1888 L1]. This was achieved through the balance of heat production and heat loss: animals with spinal cord transection were less able to regulate temperature. Therefore, the chemicals released from leucocytes increase the set-point of body temperature through their action on the central nervous system. The body increases heat production and decreases heat loss to generate a fever. This remains our understanding of fever today [Hamlin 2014].

1.1.2 History of the treatment of fever: Historically, as fever and disease states have been semantically associated, any disease was thought of and managed like fever. Alexander the Great was prescribed cool baths for his febrile illness. Willow leaves were used by Hippocrates, and by Egyptians and Assyrians before him - willow bark and leaves have

subsequently been found to contain salicylic acid. In the 19th Century the treatment of malarial fever through willow bark derived salicylic acid became prevalent following the description of its use by Reverend Edward Stone [Stone 1763]. In his address to the American Medical Association in 1896, Osler (despite being a contemporary and colleague of Welch) proclaimed “*Humanity has but three great enemies: fever, famine and war; of these by far the greatest, by far the most terrible is fever.*” [Bryan 1996]. By the mid-19th century salicylic acid was purified and manufactured industrially. Acetylsalicylic acid was discovered by Felix Hoffman working for Bayer to reduce the gastric side-effects of salicylic acid. Although initially disregarded for the ‘weakening effects on the heart’, aspirin became popular in the treatment of rheumatic fever [Dresler 1899; Miner 2007].

Yet fever has not always been considered detrimental: the ancient Greeks also believed the increased heat of fever could ‘cook’ the disease out of the patient. Hippocrates perversely observed fever had a calming effect in epileptics. Thomas Sydenham, the 17th Century English physician, claimed “*Fever is a mighty engine which Nature brings into the world for the conquest of her enemies*”.

The most fervent exploration of the beneficial effects of fever came from an unlikely source: the management of the general paresis of the insane (neurosyphilis). Pinel and Esquirol in the 19th century described the beneficial effects of fever on insanity. The psychiatrist Rosenblum induced fever using malaria and typhoid as a potential treatment of psychoses. This practice was explored more thoroughly by the Austrian neuropsychiatrist Julius Wagner-Jauregg. He treated patients with neurosyphilis using blood from patients with malaria to induce a fever. Seven to 12 days later, the malaria was treated with quinine. The reported remission rates were better than conventional treatments of the day – iodine, mercury and arsphenamine [Wagner-Jauregg 1936]. This led to the award of the Nobel Prize for Medicine to Wagner-Jauregg in 1927. The advent of antibiotics, the bioethical movement post Nuremberg and Wagner-Jauregg’s associations with the Nazi party, drove the theory

that fever could be harnessed to cure disease away from the fore-front of clinical medicine [Whitrow 1990; Tsay 2013].

Fever is not only a human phenomenon: we have evolved with it. Clues regarding the role of fever in disease can be gained from animal biology. In the following section I summarise the knowledge gained from animal experiments to inform us regarding the risks and benefits of fever.

1.2 Comparative biology

The evolution of fever can be traced back to 600 million years ago [Romanovsky 2007] (Figure 1.1). It is worth noting that plants also increase their temperature following infection with fungi and viruses. This is due to increased respiration: it is not known whether this increase in temperature is simply a by-product of the exothermic oxidative process or whether it has a secondary protective effect against infection [Farkas 1955].

That temperature modulation is a relatively primitive mechanism to influence the host-pathogen arms race can be evident from bees. The heat-sensitive fungus *Ascophaera apis* infect honeybee larvae at 30°C. In response to infection honeybees change their activity levels to increase the hive temperature to 33-36°C. This prevents infection from spreading. This temperature response has been harnessed by other pathogens – the mite *Varroa destructor*, also induces a hive temperature increase. *Varroa destructor* multiplies better at this higher temperature and therefore uses its response to its own advantage [Starks 2000; Hou 2016].

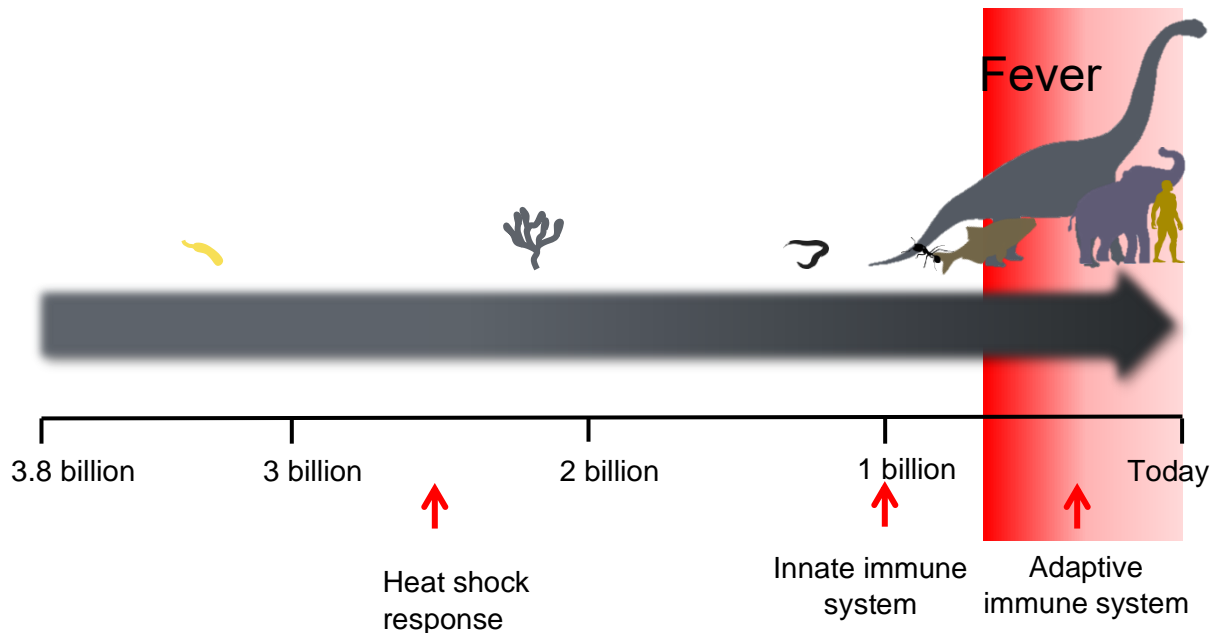
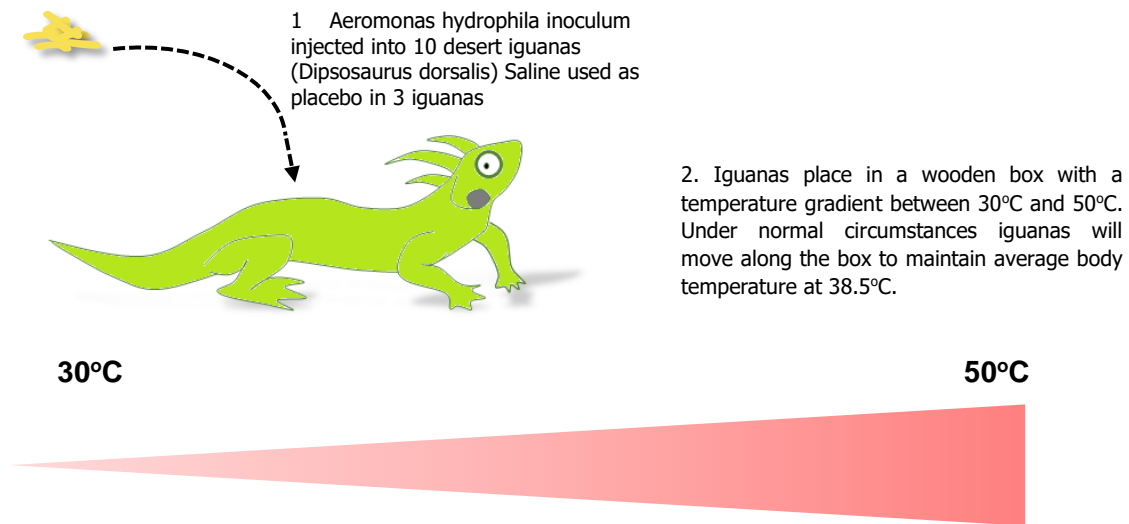


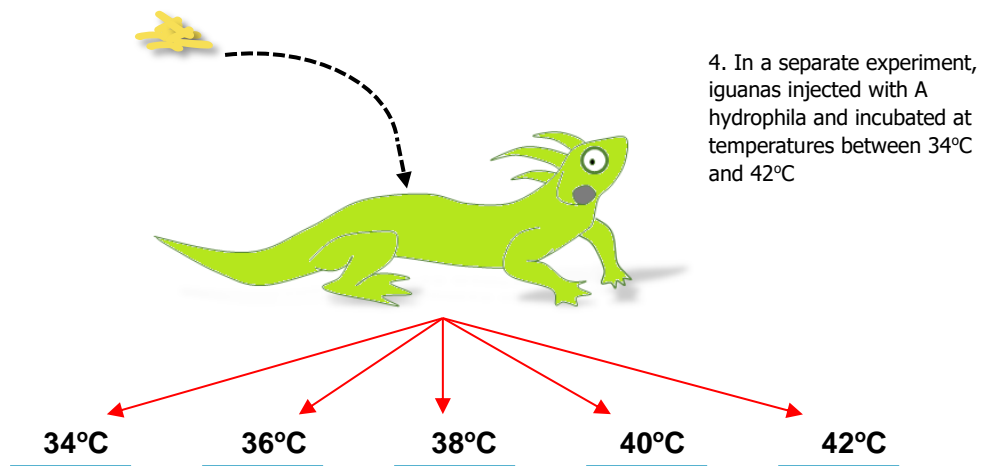
Figure 1.1: The evolution of fever. Much of the knowledge about the evolution of fever come from phylogenetic studies. The grey arrow shows the evolution of species – bacteria evolved over 3 billion years ago; multicellular organisms over 2 billion years ago. Nematodes evolved 1.2 billion years ago followed by the Cambrian explosion, during which most animal phyla appeared. The primitive heat shock response evolved 2.5 billion years before, as life was exposed to extreme temperatures. This allowed organisms to adapt to the environmental conditions, through the increased expression heat shock proteins (HSPs). HSPs act as chaperones to either protect proteins from heat damage or transport denatured proteins to organelles for degradation. Fever appeared as part of the innate immune response 600 million years ago along with the expansion and diversification of species, arthropods upwards in terms of phylogeny. (Adapted from Hasday 2014)

The most elegant demonstration of the use of fever as a defence mechanism was in the poikilothermic desert iguana, *Dipsosaurus dorsalis*. When injected with the bacteria *Aeromonas hydrophila*, the desert iguana raised its body temperature by preferentially spending time in the heated end of a temperature graded box. When an elevation in temperature is prevented by placing the iguana in a constant temperature environment, those maintained at 34 and 36°C had higher mortality rates than those who were maintained at 40 and 42°C [Vaughn 1974; Kluger 1975] (Figure 1.2). Subsequently the presence of

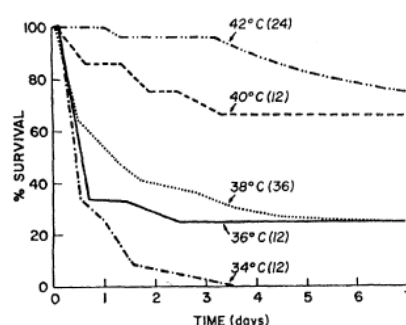
Figure 1.2: Seminal experiments carried out by Kluger and colleagues in the desert iguana, *Dipsosaurus dorsalis*. Iguanas injected with bacteria increased their body temperature by spending more time at a higher ambient temperature. If the rise of temperature was restricted by incubating at constant low temperature, iguanas showed a decrease in survival.



3. Iguana temperature monitored continuously. Between 4-6 hours after injection with *A. hydrophila*, the 10 desert iguanas increased their body temperature by 2°C. The 3 iguanas injected with saline did not.



5. Survival curves for iguanas incubated at different temperatures. Iguanas incubated at 34°C all died. Survival improved with incubation temperatures, with the greatest proportion surviving if incubated at 42°C. (graph copied from Kluger 1975)



fever has been demonstrated in lower and higher order animals, including arachnids [Cabanac 1980], fish [Reynolds 1976], amphibians [Kluger 1977], birds [D'Alecy 1975] and mammals [Stitt 1973; Urison 1993], including primates [Chan 1997]. The benefit of fever has also been demonstrated in some of these species. For example, goldfish (*Carassius auratus*) and sockeye salmon (*Oncorhynchus nerka*) are more likely to survive following infection if exposed to higher temperatures [Covert 1977]. In rabbits, fever following infection with *Pasteurella multocida* was shown to have a survival effect. Survival improved up to a temperature increase of 2.25°C above baseline but declined for any further increases in temperature beyond that. The increase in temperature did not have any direct effects on bacteria in vitro, suggesting that the survival effect of fever was not due to a direct effect of an increase in temperature, but more likely a chemical driven process, or a potentiation of immune mechanisms [Kluger 1978]. Treatment of febrile rabbits and mice with aspirin is associated with an increase in mortality, which reaches statistical significance following meta-analysis [Jefferies 2012]. In a randomised controlled trial involving a sheep model of sepsis, febrile sheep had better respiratory function (measured as a PaO₂/FiO₂ ratio), improved lactate clearance, and longer survival times compared those whose temperature was controlled using paracetamol and external cooling [Su 2005].

The evolutionary conservation of fever points to a net survival benefit. This has been demonstrated successfully in many animal species, even in poikilotherms. Given the possible role in fighting disease, and fever's evolution with the sophistication of the immune system, fever is thought of as part of the immune response. How does fever aid in the fight against disease? The benefit may be secondary to the effect of fever on the pathogen, the host response, or combination of the two. In the following section I will describe the effect that fever has on pathogens, and the innate and adaptive arms of the immune system.

1.3 The immune biology of fever

1.3.1 Effect of temperature on pathogens: Pathogens can be temperature sensitive, demonstrating optimal multiplication rates at specific temperature ranges [Ellner 1966]. This has been demonstrated *in-vitro*: bacteria have species-specific optimal temperatures for survival and replication in vitro [Tsuji 1982; Hasday 2014]. This temperature dependence may determine the host that the pathogen infects, and vice versa; the tissues infected; and the seasonality of infection: it is part of the arms race between the host and the pathogen. *Coxiella burnetii* grows best in chick embryos at higher temperatures and is commonly carried in animals with higher body temperatures than humans [Rodbard 1981]. As previously described, honeybees increase hive temperature to protect themselves from the chalk brood fungus (*Ascophaera apis*), but consequently become susceptible to infection by the Varroa destructor mite, who prefer warmer temperatures. [Starks 2000; Hou 2016]. Optimal temperatures determine the tissues affected by certain pathogens: syphilitic chancres appear in tissues with lower temperatures (skin, genitals), while raising the temperature of these tissues retards the number and growth of these lesions. Similar correlation is seen with local body temperature and organism density with *Mycobacterium leprae* infection. Mycotic infections prefer the lower temperatures of the peripheral extremities [Rodbard 1981]. Rhinovirus grows optimally at 33°C, and therefore grows best in the upper airway epithelium and may explain the seasonal variation in infections rates [Ikaheimo 2016]. Influenza virus is more stable at lower temperatures and transmission rates improve in cold ambient temperatures [Lowen 2014].

1.3.2 Effect of fever on the host immune response: Fever is not only part of the immune response, as described above, but also plays a vital role in enhancing the response itself (Figure 1.3). The effect of temperature starts at the level of barrier defence: the respiratory epithelial cilia beat frequency is directly proportional to temperature [Smith 2011]. Fever may

aid the muco-ciliary escalator in extruding pathogens from the respiratory tract, although this effect has yet to be demonstrated *in vivo*.

Fever feeds forward to modulate the innate immune response. This response is not simply an effect of the temperature increase associated with fever. Mice exposed to fever range hyperthermia (38.8°C) do not show any increase in the level of acute phase cytokines compared to controls. However, when the mice were injected with lipopolysaccharide, there were increases acute phase cytokines secreted from macrophages, such as IL-1, IL-6 and TNF- α . This increase however varied according to the strain of mice used. Also, the effect was opposite when murine cells from the same species were heated up *in vitro* in the presence of lipopolysaccharide – cytokines levels were lower in cells that were heated compared to those that were not [Ostberg 2000]. This differential response of cytokine release to hyperthermia in the presence of lipopolysaccharide suggests the cellular response of fever is complex, with both direct effects of temperature on cytokine release, but also potential indirect effects of temperature through other chemical mediators (hence different responses *in vitro* and *in vivo*). Part of the fever effect is mediated via heat shock proteins (HSPs) such as HSP 70 and HSP 90. Whilst HSP 70 is largely an intracellular protein, fever can lead to its extracellular release. Extracellular HSP 70 is a Danger Associated Molecular Pattern (DAMP) stimulating Toll-like receptors 2 and 4 to initiate an innate immune response. Intracellular HSP 70 has several roles including the induction of nitric oxide synthase in macrophages to aid phagocytic destruction, and the sustained activation of macrophages in response to a lipopolysaccharide (LPS) stimulus. HSP 90 plays a crucial role in T-cell migration by binding to integrins following a rise in temperature to 40°C [Lin 2019]. However intracellular HSP 70 (along with other heat shock proteins) can also have an anti-inflammatory role, again pointing to the self-regulatory role of fever [Gupta 2013; Hasday 2014]. Similarly, fever can also inhibit the release of the DAMP HMGB-1 from macrophages, thereby reducing inflammation [Hasday 2014].

Neutrophil numbers are increased by fever. An increase in G-CSF expression leads to an increase in neutrophil numbers through increased bone marrow stimulation [Ellis 1985]. Neutrophil recruitment to tissues is increased by a fever grade temperature induced increase in cytokine CXCL expression, and changes in endothelial factors, such as extracellular signal related kinase (ERK) and p38 mitogen activated protein kinase [Tularpurkar 2011]. However, this fever induced response may not always be beneficial: ARDS mice models show increased disease severity with increased neutrophil migration when exposed to fever range temperatures [Tularpurkar 2012; Hasday 2003].

Natural killer (NK) cell cytotoxic activity is also enhanced by whole body hyperthermia. This has largely been demonstrated in the context on tumour immunity. This is mediated not by an increase in the numbers of specific NKG2D receptors, but clustering of these receptors. In addition, expression of the ligand to this receptor on tumour cells (MHC class I related chain A) is up-regulated by fever range temperatures [Ostberg 2007].

Fever enhances antigen presentation by dendritic and Langerhans cells. Expression of cell surface MHC molecules is increased on dendritic cells by febrile temperatures. Migration of antigen presenting cells to lymph nodes is augmented through the increases in CCR7 responsiveness and chemotaxis along a gradient of the CCR7 ligand CCL21. The antigen presenting cells also localise to areas that enhance contact with lymphocytes in the high endothelial venules [Evans 2015].

Fever increases T cell trafficking, especially circulation of T cells through lymph nodes, to be stimulated by antigen presenting cells. Part of this is a result of changes in the lymphocyte cytoskeleton, such as through HSP 90 regulated integrin changes [Lin 2019]. Lymphocyte endothelial interaction is also increased, particularly in high endothelial venules of lymph nodes. This is mediated by IL-6, and is thus a key mechanism by which the innate immune system activates the adaptive immune system. Once in the lymph nodes, T cell activation is also enhanced by fever: this is thought to be brought about by pre-activation of the T cell receptor complex. CD8 cells show greater differentiation, enhanced cytotoxic function and

increased IFN- γ release following exposure to febrile temperatures *in vitro*. Similarly, the threshold for CD28 stimulation for CD4 T cell production of IL-2 is reduced by fever [Evans 2015]. The effect of fever on the various immune cell types is summarised in Figure 1.3.

Clinically, temperature is associated with a switch from a neutrophilic to a lymphocytic phenotype: hypothermia is associated with a relative lymphopenia on day 4 to 7 in critically ill patients, during which the lymphocyte count would normally rise. This may signal the importance of fever as part of the switch from a primarily innate to a primarily adaptive immune response [Drewry 2015].

Interestingly, the action of antibiotics seems to also have temperature sensitivity: *in vitro* experiments have shown that the rate of antibiotic induced bacterial death varies according to temperature. The rate of bacterial death increases with temperature within the 37 to 41°C temperature range, suggesting a beneficial effect of fever even in the era of antibiotics [Mackowiak 1981].

The above evidence all points to the role of fever in potentiating the response of the immune system. Although inferring the effects of fever on the immune system, most of the *in vitro* experiments investigate the effect of temperature. Increases in body temperature certainly plays a role in the protective effects of fever: this is evident from Kluger's experiments in the desert iguana. Although humans may demonstrate some heat seeking behaviour, we are primarily homeotherms: body temperature is maintained within a narrow range regardless of the environment. To understand the physiological effects of fever in humans it is important to understand the mechanisms that maintain the body temperature within a narrow range and how this is overridden during fever. I will also explore the definitions of fever as used in clinical studies and by regulatory bodies.

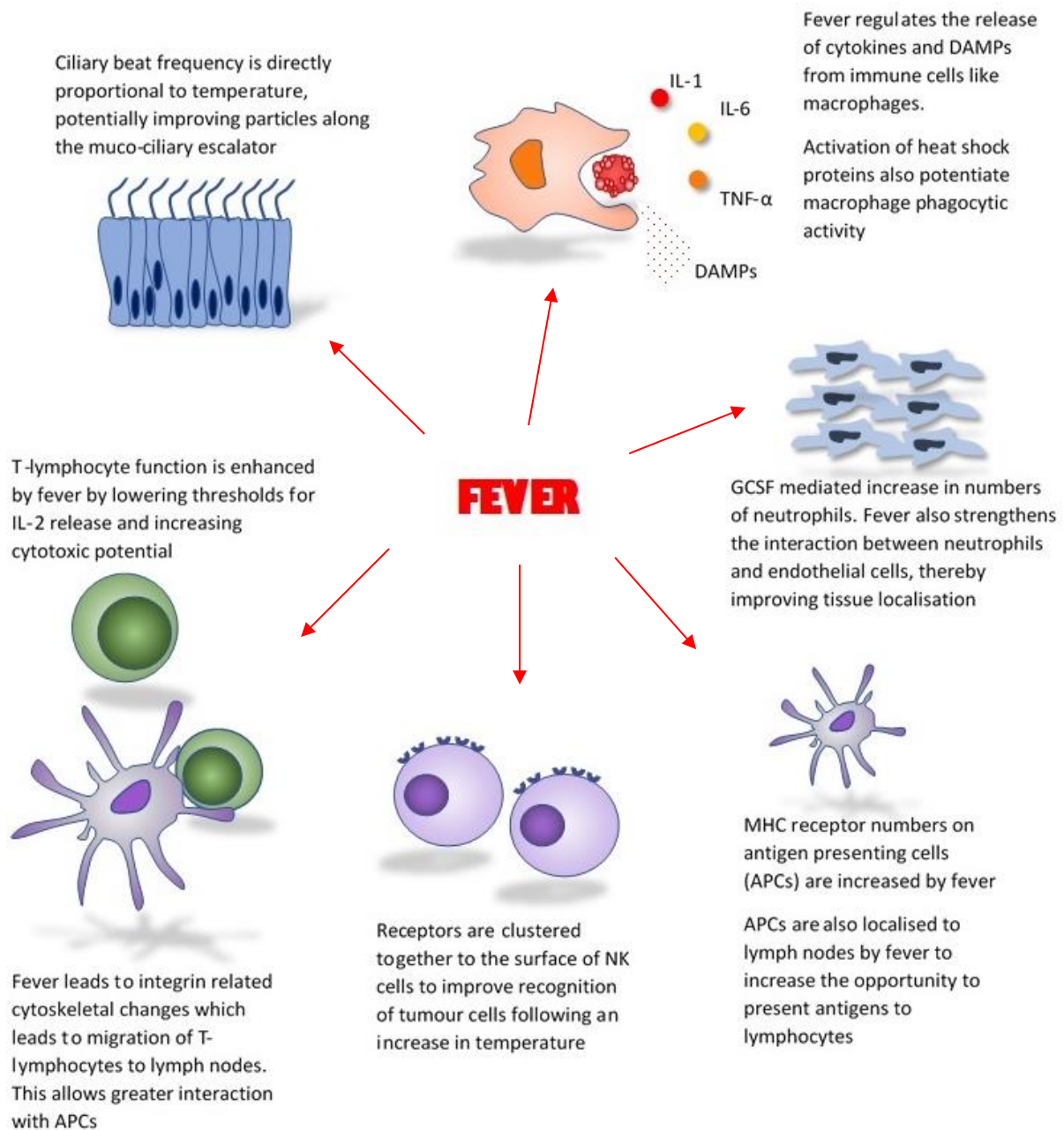


Figure 1.3: The immune effects of fever. Fever has widespread effects across the innate and adaptive immune response. Most of the immune effects of fever are to potentiate the response - a feed-forward effect given that fever itself is part of the immune response. However, fever also serves to regulate the immune response: release of cytokines and DAMPs are increased but also decreased, suggesting that fever may serve to switch itself off, in a time or context dependent manner.

1.4. Temperature regulation in humans

Whilst many of the *in vitro* effects of fever regard fever as synonymous with a temperature increase, *in vivo* fever is a cytokine driven increase in body temperature. Dissociating the effects of cytokines and the temperature increase *per se* is difficult. The temperature increase alone is clearly instrumental in some of the immune mediated effects and the survival benefit: this is evident from Kluger's experiments on the desert iguana. Although humans do demonstrate some heat seeking behaviour, human fever largely relies on an endogenous increase in temperature. To understand the effects of a fever-driven temperature rise, it is important understand how temperature is regulated normally in humans and how temperature regulation changes during fever.

1.4.1 Normal thermoregulation

Humans maintain their body temperature within a restricted temperature range, with circadian variations [Reinberg 1975; Mackowiak 1992]. This is known as homeothermy. The thermoregulatory mechanism requires an afferent pathway that senses temperature, central integration of the thermal information and an efferent pathway that allows the modulation of temperature [Hasday 2014].

In order to maintain homeothermy, the regulatory mechanism must prevent large deviations in the core body temperature. Therefore, cutaneous thermoreceptors sense changes in the environmental temperature and send signals to the central thermoregulatory centre. Thermal sensing neurons contain temperature dependent cation channels of the transient receptor potential (TRP) superfamily. Different temperature dependent TRP channels are active at different temperature ranges. The cutaneous thermal sensing neurons synapse in the dorsal horn of the spinal column, with thermal pathways extending up to either the thalamus, or the lateral parabrachial (LPB) nucleus of the pons. The signals from the thalamus are transmitted to the sensory cortex, but do not play a role in thermoregulation. However, the

LPB neurons transmit signals to the pre-optic area of the hypothalamus, which includes the thermoregulatory centre [Hasday 2014].

The proposed model of central integration involves the balance of activation and inhibition between a group of temperature insensitive pacemaker neurons and a group of warm sensing neurons. The pacemaker cells have tonic activity, inhibiting heat loss mechanisms. Increase in environmental temperature is sensed by the cutaneous thermoreceptors, eventually leading to the activation of warm-sensitive neurons in the pre-optic area. This has two effects: the tonic activity of the pacemaker neurons is reduced, leading to the release of heat loss inhibition; and there is a direct activation of heat loss through sweating and inhibition of heat production. When there is a decrease in environmental temperature, the warm-sensitive neurons are inhibited. This leads to a release of inhibition of the pacemaker cells, and as a subsequent increase in heat production and prevention of heat loss (Figure 1.4) [Hasday 2014; Morrison 2019].

1.4.2 Effector mechanisms for maintaining temperature

Mammals, as homeotherms, maintain their body temperature even if the environmental temperature rises or falls outside a narrow thermo-neutral zone (Figure 1.5a). Body temperature is maintained by the balance between heat production (thermogenesis) and heat elimination. Mammalian thermoregulation does also include behavioural changes, for example, changing body position or moving to a warmer area to conserve heat. This suggests that thermoregulation may involve wider neural circuitry, including the limbic system [Hasday 2014; Morrison 2019].

Thermogenesis, or heat production, requires energy. In biological systems energy is produced by the metabolism of carbohydrates, fats and proteins. The process is coupled to the electron transport chain in the mitochondria - through a sequence of mechanistically complex steps energy from the fuel is transferred to the chemical bond between adenosine

diphosphate (ADP) and phosphate, forming adenosine triphosphate (ATP). ATP is then dephosphorylated to release energy for endothermic chemical processes, e.g. during muscle contraction. A proportion of the energy from ATP is released as heat. Although this may be viewed as 'wasted' energy, it is a major mode of thermogenesis and utilised to maintain temperature when exposed to temperatures below the lower limit of the thermo-neutral zone, through shivering. Similarly, body temperature rises during exercise.

Over the last 30 years, two other phenomenon that generate heat through non-shivering mechanisms, have come to light. Both involve the slow leak of ion gradients across membranes: the leak of calcium ions out of the sarcoplasmic reticulum in muscle tissues, and the leak of proton gradients in the mitochondria. In the former, heat is generated as Ca^{2+} ATPase activity increased to maintain the high concentration of calcium in muscle sarcoplasmic reticulum. This is not accompanied by any muscle contraction. This is used by fish such as swordfish and marlin in maintaining temperature in cold waters, using specially adapted muscle cells. Ducklings also increase the expression of Ca^{2+} ATPase in the sarcoplasmic reticulum in the winter, suggesting this as a mechanism in generating heat. It is this mechanism that is behind heat generation in malignant hyperthermia: calcium leak due to mutations in the ryanodine receptor associated calcium channels in the muscle leads to increase in Ca^{2+} ATPase activity, and a 5 fold increase in heat production [de Meies 2001].

The leak of protons across the gradient in the mitochondria leading to heat generation, known as mitochondrial uncoupling, is typical to mammals only. The electron transport chain works by creating a proton gradient between the mitochondrial matrix and the inter-membrane space. It is this gradient that is required for the phosphorylation of ADP to ATP. However, this coupling between the electron transport chain and ATP synthesis is not perfect. Background proton leak occurs reducing the gradient created. The energy from the loss of this gradient from leak is dissipated as heat. In addition to background or basal proton leak, this leak can be induced by the activation of uncoupling proteins [Busiello 2014].

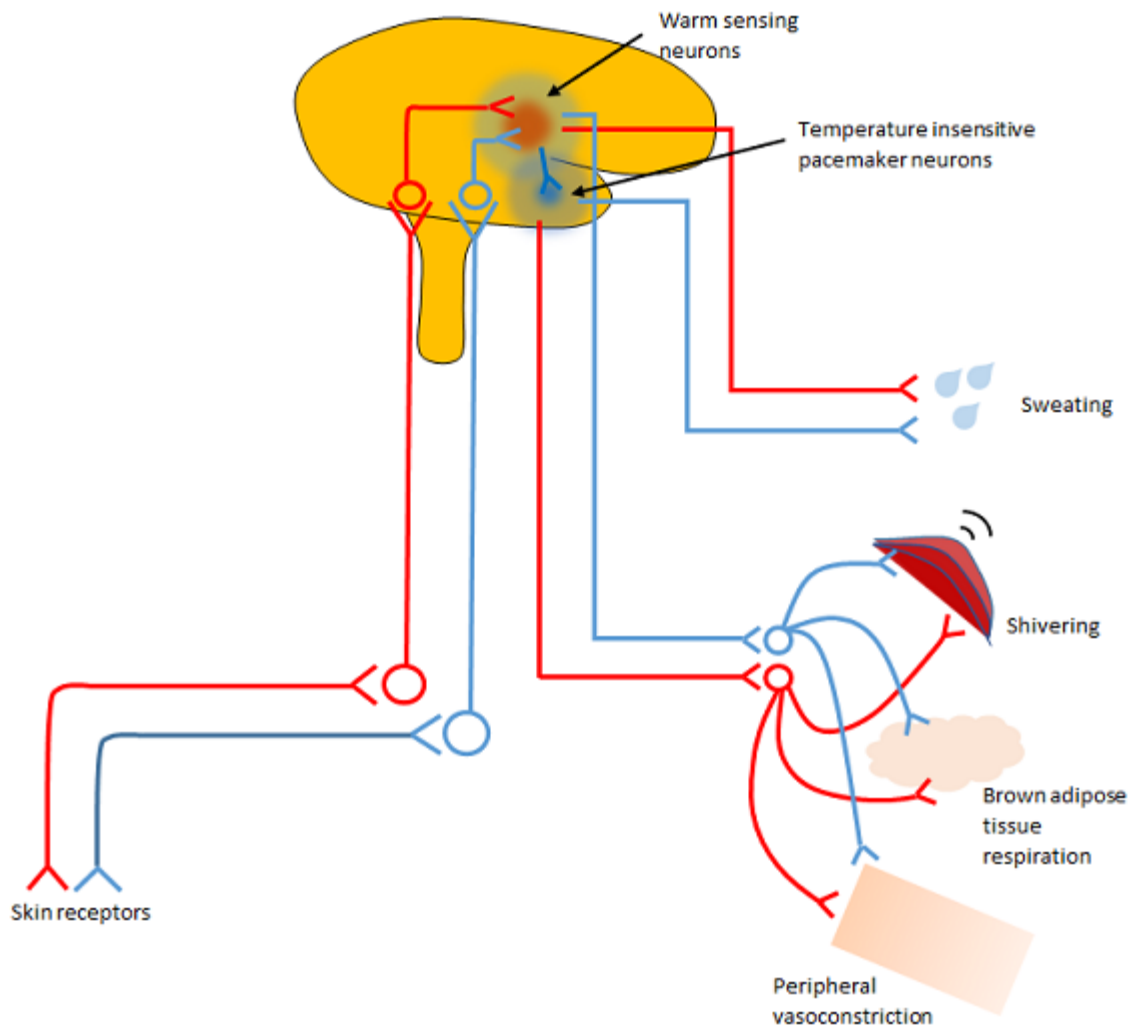
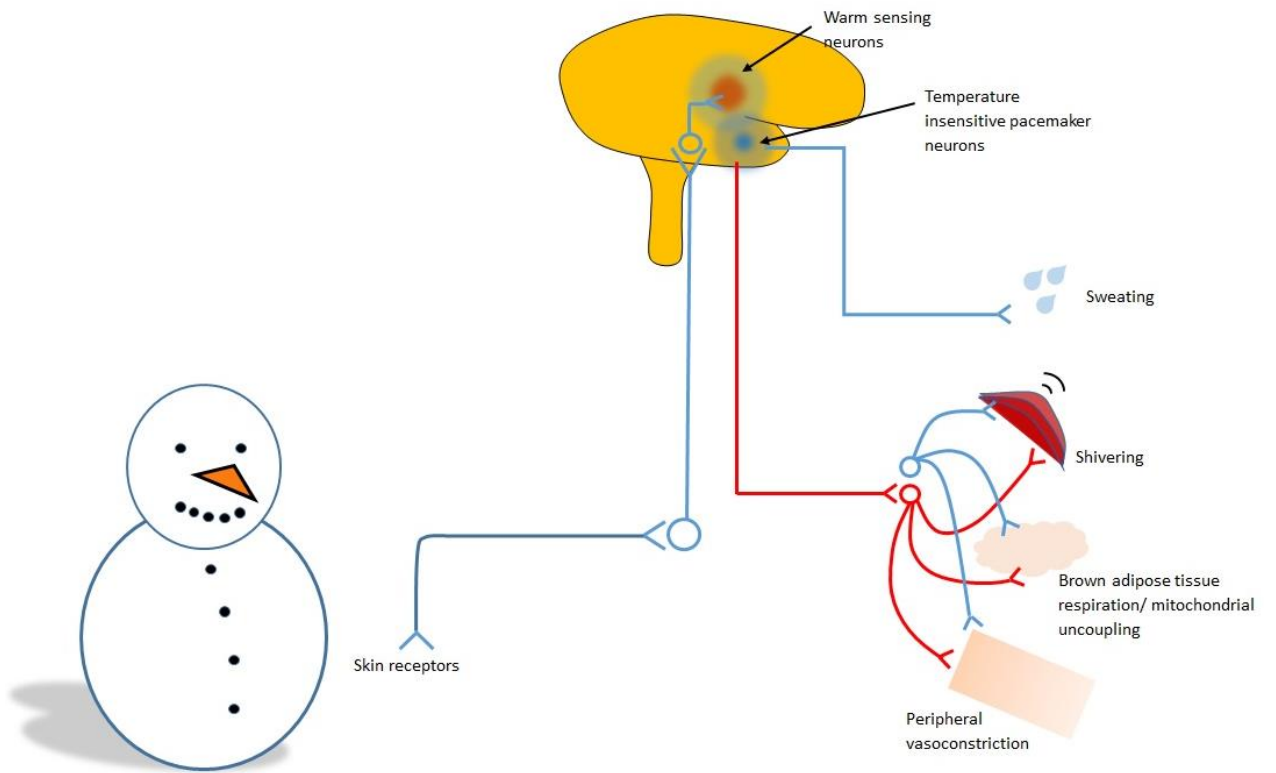
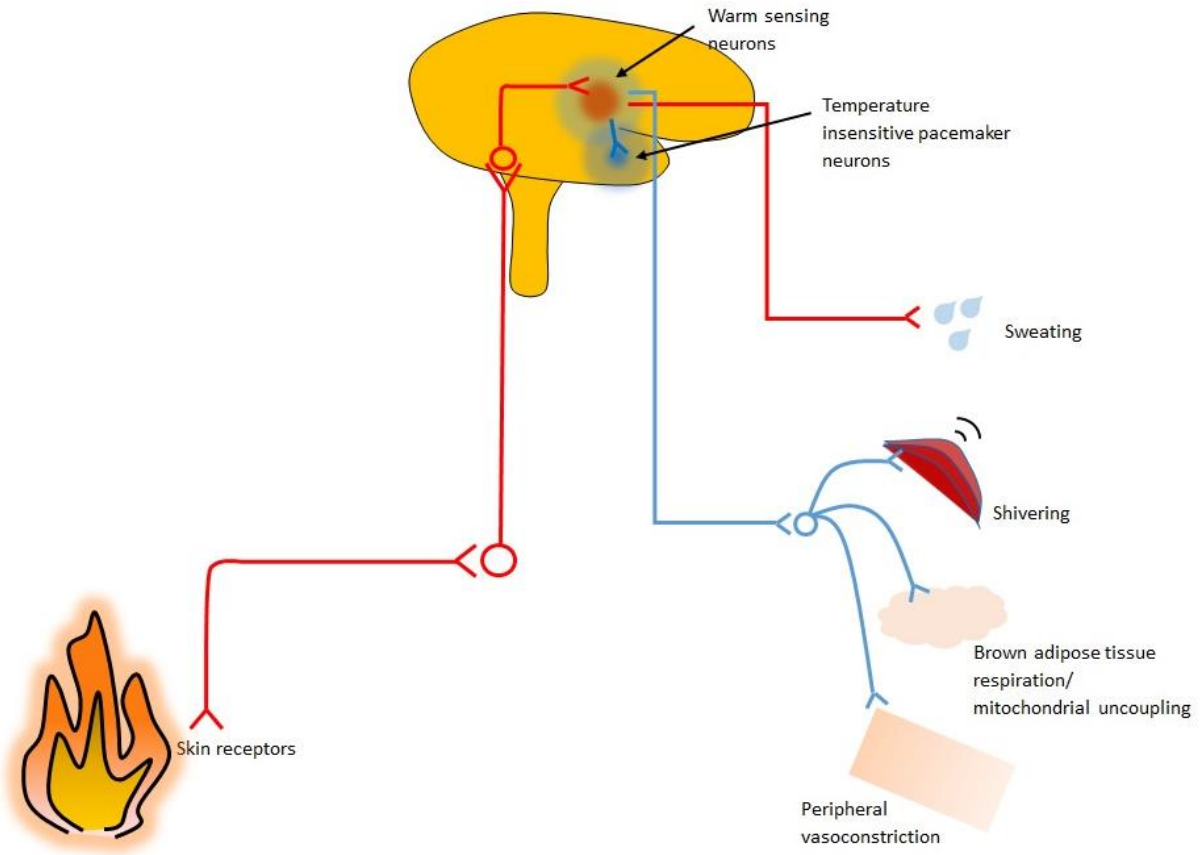


Figure 1.4: Thermoregulatory pathways in humans. The schema shows all the afferent and efferent pathways. Warm and cold skin receptors both relay signals to the warm sensing neurons in the hypothalamus. At baseline, body temperature is maintained by the temperature insensitive pacemaker neurons, which maintain heat production and conservation. When the warm sensing receptors are activated, the signal is relayed to the warm sensing neurons (**overleaf**, top). Three pathways are activated following this: (i) the temperature insensitive pacemaker neurons are inhibited, (ii) the heat production and conservation mechanisms are inhibited, and (iii) heat losing mechanisms such as sweating are activated. When cold sensing receptors are activated, the opposite happens (**overleaf**, bottom): inhibition of the temperature insensitive pacemaker neurons is removed, heat production and conservation is increased through shivering, peripheral vasoconstriction and mitochondrial uncoupling in brown adipose tissue, and heat losing pathways are inhibited.



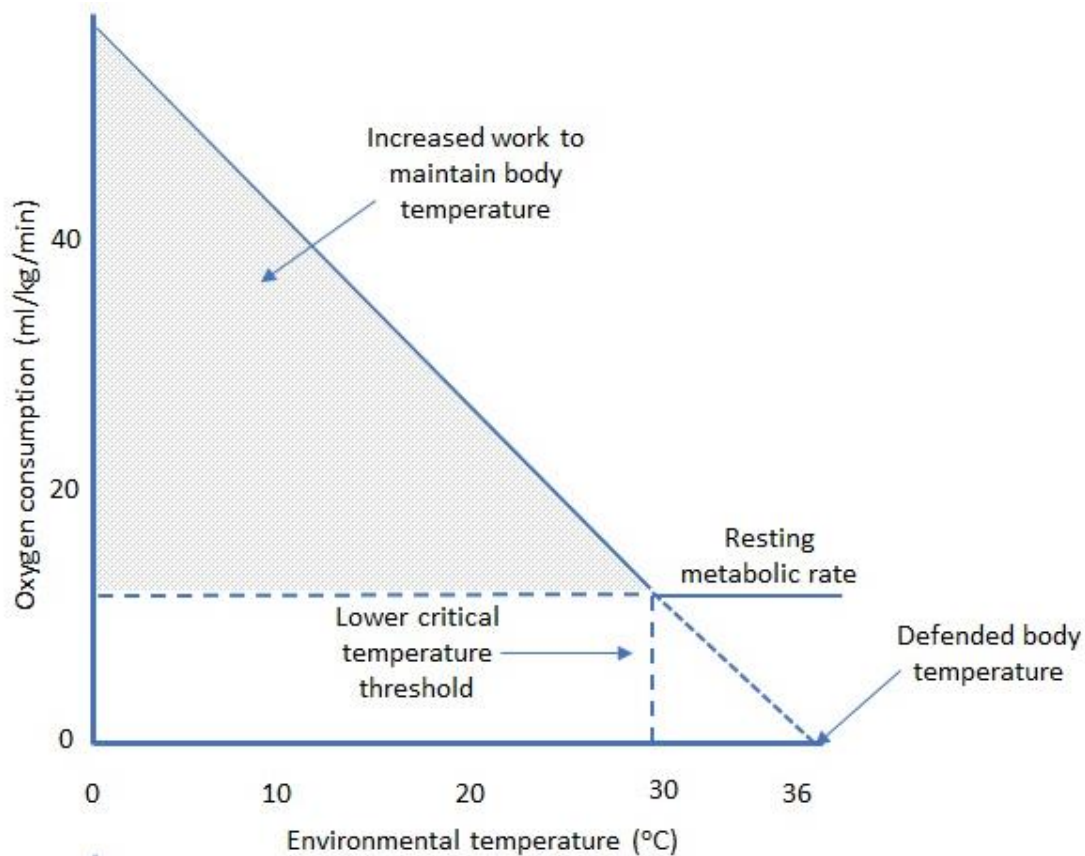


Figure 1.5a: Schematic diagram showing work required to maintain body temperature. Body temperature is maintained by the resting metabolic rate within the thermoneutral zone. The energy required to maintain body temperature increases as the environmental temperature drops below the lower critical temperature threshold, outside the thermoneutral zone. (Adapted from Cannon 2004)

Uncoupling is a mechanism by which brown adipose tissue in particular produces heat [Arbuthnott 1989]. The induction of uncoupling proteins could lead to short term increase in heat production for example during fever (uncoupling proteins can also regulate the maturation and differentiation of brown adipose tissue – this used to maintain heat stores during winter hibernation). This form of non-shivering thermogenesis is mediated through noradrenaline signalling, in response to detection of free fatty acids. It is possible that if glycogen stores are scarce, thermogenesis switches from shivering to non-shivering thermogenesis [Cannon 2004].

The exact contribution of mitochondrial uncoupling in the generation of fever is difficult to study in humans due to the small amount of increase in proton leak that is required to increase temperature into the fever range. Most studies have relied on the uncoupling protein 1 (UCP1) knockout mice, or the using toxins such as dinitrophenol in rodent models to induce mitochondrial uncoupling. The results have been variable – while some authors have shown that UCP1 knockout mice could still maintain a febrile response to IL1 [Okamatsu 2006], others have shown a blunted response in oxygen consumption and temperature rise following a dinitrophenol injection in already febrile rats [Greco 2014].

A likely explanation of these variable results is that there are three mechanisms through which body temperature can be raised: shivering and non-shivering thermogenesis, and heat conservation through reduction of heat loss at the body surface. In sub-thermoneutral environments, sympathetic neuronal activity leads to cutaneous vasoconstriction. This reduces heat loss from the body surface. Concomitantly, vasodilation occurs elsewhere in the body to balance the distribution of blood, thought to be regulated by baroreceptor reflexes. This relative increase in blood supply to the visceral organs, including skeletal muscles brown and adipose tissue may increase heat production through shivering and non-shivering thermogenesis respectively [Morrison 2019].

Not all three mechanisms may need to be deployed to generate a fever. Romanovsky theorised the existence of a central co-ordinator that determines the thermoregulatory mechanisms used at any time [Romanovsky 2007]. There may not be a single hierarchy that determines which mechanism is employed - this may depend on several factors including the remaining energy demands placed on the mammal at the time. Evidence that heat production and heat loss can be independently controlled come from rat studies. Tanaka et al demonstrated dissociation between the central neural pathways that control peripheral vasoconstriction response in rat tails (excitatory signals from the rostromedial pre-optic region to the medullary raphe) and thermogenesis (excitatory pathway from the rostromedial pre-optic area via a synapse in the dorsomedial hypothalamic nucleus, to the medullary

raphe) [Tanaka 2013]. This suggests that sympathetic activity may not have an 'all or nothing' response in preventing heat loss and promoting heat production.

It may be possible that reducing heat loss contributes relatively more to raise the temperature into the febrile range in smaller animals, rather than using energy to generate heat. Basal metabolism increases according to body weight between mammalian species by the power of 0.75 of weight in kg. The surface area of mammals increases by a power of 0.67 of their weight in kg. Therefore, to maintain a constant body temperature across species against the surface heat loss of a relatively larger body surface area, smaller animals may conserve heat better rather than spend energy on heat generation. Whilst this phenomenon has been used to describe differences in thermoregulation between mammalian species, it is possible that these differences exist between infant and adult humans. Babies are born at a 1/20th the weight of an average adult human. The relative contribution of heat loss reduction could be greater compared to thermogenesis in children, particularly infants. Of note, preterm and very low birth weight neonates are unable to defend their body temperature by increasing metabolic activity. In neonates born between 29 and 35 weeks gestational age (weighing 0.8-1.85kg) Sauer et al demonstrated that the thermoneutral temperature (i.e. the environmental temperature at which the body temperature is defended without increasing metabolic activity) increases, thereafter becoming reliant on weight and age [Sauer 1984].

1.4.3 Thermostatic change and fever

In fever, body temperature can increase independently of the external environmental temperature signals transmitted by the cutaneous afferents. External environmental temperature signals can still influence thermoregulatory mechanisms: for example, shivering may occur during external cooling to try and defend the body temperature from falling [Mayer

2001]. This suggests that homeostasis is not lost in fever, merely regulated. According to Kluger, “fever is an example of a regulated change in homeostasis.” [Kozak 2000].

Two hypotheses exist regarding the mechanism behind this: either the regulatory set point is changed (thermostat is set higher), or the sensitivity of the regulatory mechanisms change i.e. warm sensitive neurons become less responsive and cold sensitive neurones become more responsive (gain of response is changed). In a set of experiments, Cabanac and Massanet demonstrated the former as being the primary mechanism of temperature change in fever. The investigators first placed subjects without fever in hot (40°C) and cold (30°C) baths (external stimulus to control temperature). At the same time, they had the subjects place their hand in a separately temperature-controlled glove. The glove temperature was increased every 2 minutes. The subjects were asked to record their preferred glove temperature. As their body temperature fell, the subjects preferred higher glove temperatures, demonstrating their preference for external heat to maintain a higher body temperature. This was repeated in those with fever. Were the temperature rise in fever due a change in the gain in the thermoregulatory mechanisms, then the preferred glove temperature would be expected to increase exponentially as the body temperature fell. Instead, in fever there was a change in preferred temperature, with a translational shift towards the preference of higher glove temperatures at higher body temperatures – the correlation remained linear [Cabanac 1974]. This is represented by the schematic in Figure 1.5b.

The temperature set-point is changed in fever, possibly with a change in the pacemaker neuron firing frequency, thereby increasing heat production and/or preventing heat loss. The set-point change is brought about by chemical mediators. Several endogens pyrogens and cryogens (anti-pyretics) have been identified. Most pyrogens are released during the innate immune response by cells such as neutrophils and macrophages. Examples include TNF- α , IL-1 β , IL-6 and IFN- γ . While some pyrogens are thought to act directly on the thermoregulatory centre, several pieces of evidence point to prostaglandin E (PGE₂) being

an important mediator in changing the temperature set-point in fever: (i) direct injection of PGE2 into the pre-optic area of the hypothalamus can lead to fever [Ranelis 2005]; (ii) the PGE2 receptor EP3 is expressed in the pre-optic area of the hypothalamus [Nakamura 2009]; (iii) EP3 knock out mice do not produce a fever in response to PGE2, IL-1 β and endotoxin [Ushikubi 1998]; (iv) most anti-pyretics act by inhibiting cyclo-oxygenase-2 (COX-

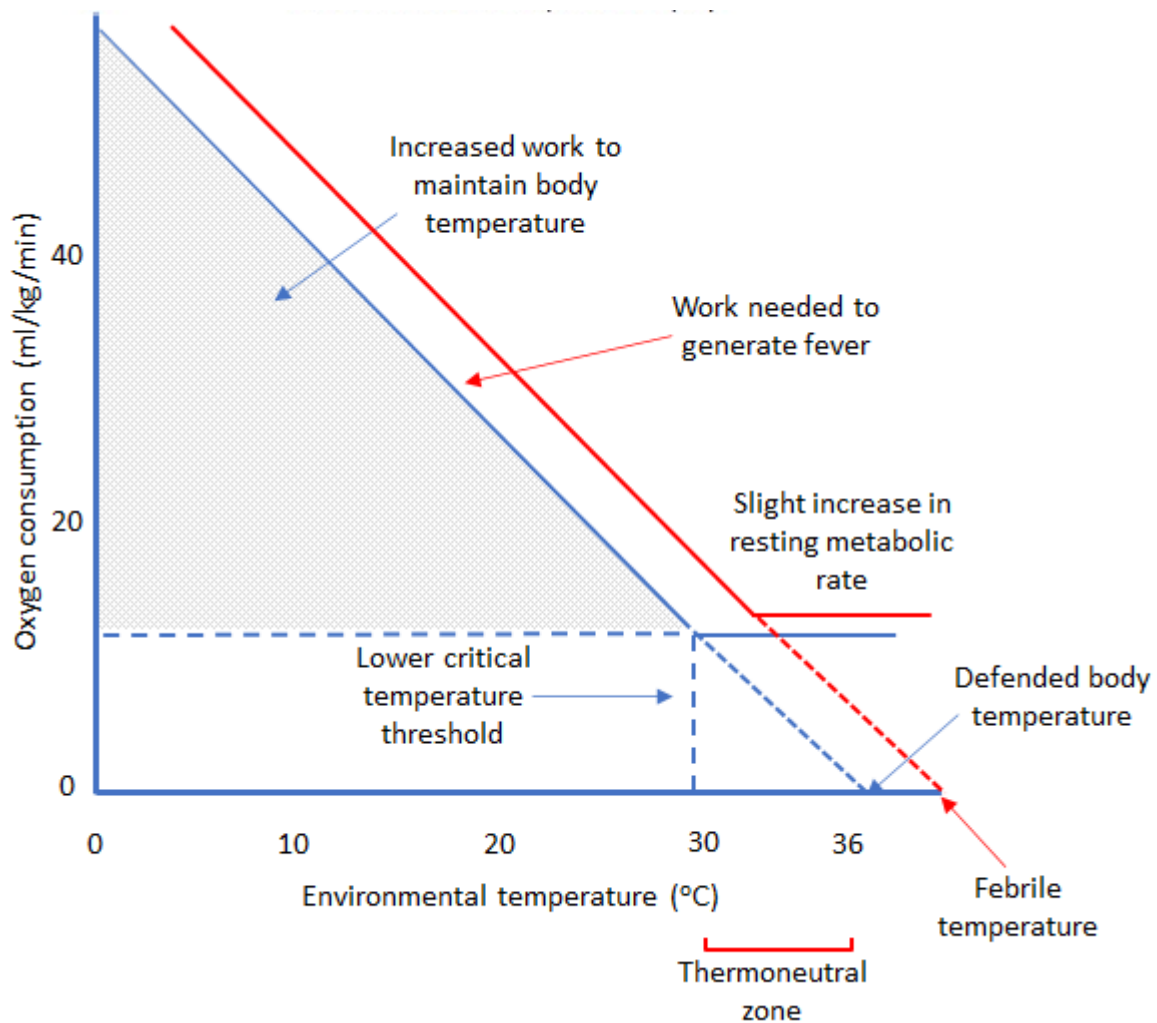


Figure 1.5b: Schematic diagram showing work required to generate a fever. With fever, body temperature is defended at a higher set-point. This requires an increase in the metabolic rate and an increase in the work if the environmental temperature is outside the thermoneutral zone. (Adapted from Cannon 2014)

2), reducing PGE2 levels, suggesting its role as a downstream mediator of fever [Simmons 2001] (v) COX-2 gene deletion in mice blocks the generation of fever post injection with

lipopolysaccharide [Steiner 2005]. The role of PGE₂ is evolutionarily conserved – salicylic acid is anti-pyretic in poikilotherms such as the desert iguana [Kozak 2000; Hasday 2014]. (Figure 1.6)

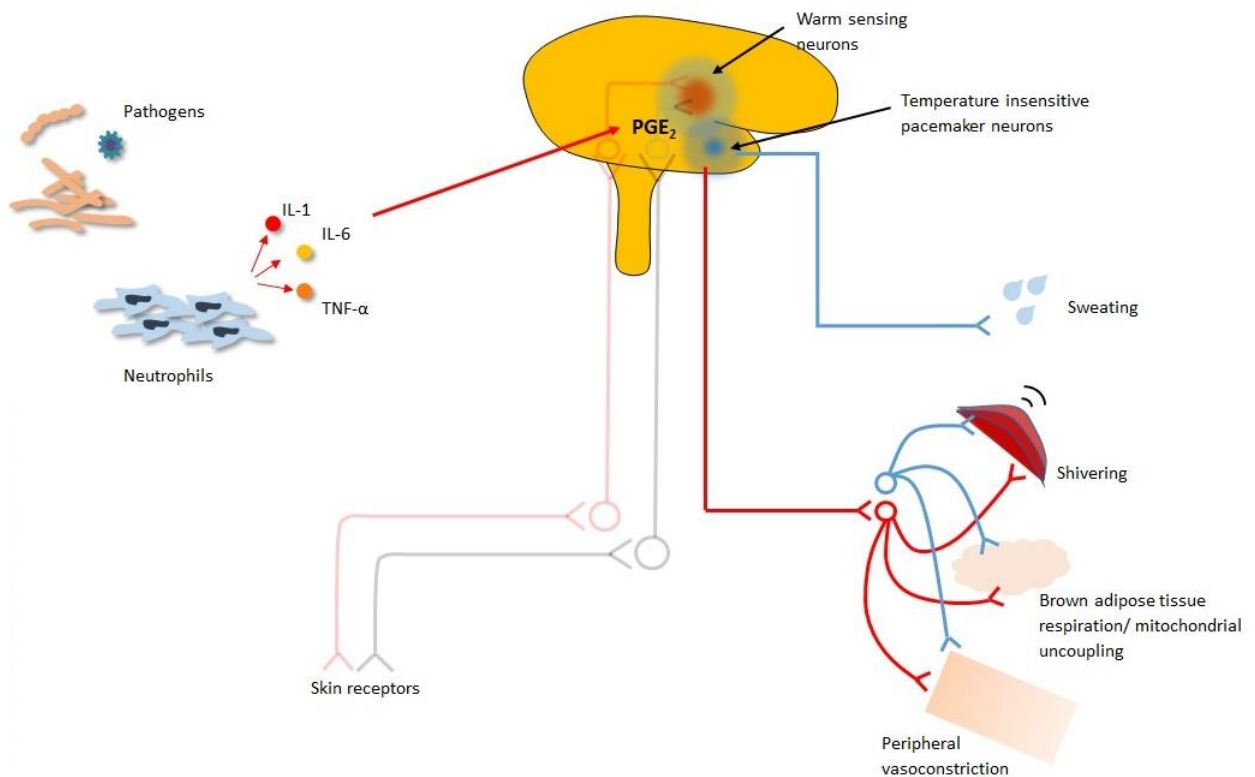


Figure 1.6: Thermoregulation in fever. The innate immune response is activated by a threat e.g. pathogen invasion. Innate immune cells such as neutrophils release pyrogenic cytokines - interleukin-1 (IL-1) and 6 (IL-6), tumour necrosis factor- α (TNF- α) etc. The pyrogenic cytokines lead to an increase in prostaglandin E₂ levels in the thermoregulatory centre of the hypothalamus. The result is an increase the thermoregulatory set-point: consequently there is an increase in heat production and conservation, and an inhibition of heat losing mechanisms.

1.4.4 What is fever in humans?

Given that fever is caused by a change in the thermoregulatory set-point, it is important to know what the normal set-point is. Human body temperature is not constant: both intra- and

inter-individual variation exists. Whilst fever can be characterised as ‘an elevation of body temperature above the normal daily variation’ [NICE 2013], pragmatically this definition is difficult to use both in clinical medicine and research. Temperature thresholds have been used to define fever since the advent of clinical thermometry in medicine. In order to define fever by temperature, it is important to establish what a normal temperature is, and what is the degree of intra- and inter-individual variation.

1.4.4.1 Normal body temperature

The most detailed exploration of human body temperature was performed by Carl Wunderlich, a 19th Century German physician. He described the result of measuring over 1 million axillary temperatures, in 25,000 human subjects. (Each recording took 15 minutes, suggesting that Wunderlich’s measurements would have taken 10,000 person days to record!). Wunderlich observed the following: 37.0°C was the mean temperature of healthy adults; there was a diurnal variation of temperature of up to 0.5°C, with a nadir between 02:00 and 08:00 hours and a peak between 16:00 and 21:00; women and children had higher temperatures than men and adults; ‘old people’ were 0.5°C cooler than younger people; and temperatures of $\geq 38^\circ\text{C}$ were suspicious and probably febrile [Wunderlich 1868].

Wunderlich’s findings have been questioned despite the description of a large data set, given the lack of computing power available to him at the time. Subsequent comparisons of one of Wunderlich’s thermometers with modern-day reference thermometers suggests Wunderlich’s thermometer read 1.4-1.9°C above reference thermometers [Mackowiak 1994]. Mackowiak described oral temperatures from 148 healthy subjects recruited for Shigella vaccine trials. He confirmed the diurnal variation in temperatures and the differences according to sex, in addition to race. In this cohort, the mean and median temperature was described as 36.8°C, with a mode of 36.7°C. There was no relationship between age and temperature between 18 and 40 years [Mackowiak 1992].

Temperature varies according to site of measurement. Peripheral sites are more influenced by environmental conditions and haemodynamic states e.g. vasoconstriction. Intravascular temperature measurements from pulmonary artery catheters are quoted as gold-standard. The invasive nature of pulmonary artery catheters limits their use – 78/139 of the ICUs who responded in the EUROBACT survey reported the use of pulmonary artery catheters for temperature measurement, with only 1 stating its use as a primary site of temperature measurement [Niven 2013b]. Central sites of temperature measurement include the oesophagus, rectum and bladder – these are common sites of measurement in intensive care unit and theatre environments [Niven 2013b]. The 95% limits of agreement (LOA) with pulmonary artery catheter temperatures and oesophageal/rectal/bladder temperatures are between $\pm 0.5^{\circ}\text{C}$ [Niven 2015]. Tympanic membrane, oral and axillary thermometers provide peripheral temperatures, generally used in ambulatory subjects (as are infra-red non-contact thermometers, although these are relatively poorly studied). A meta-analysis of the comparison between simultaneous (within 5 minutes) central and peripheral temperatures by Niven et al from 75 studies (8682 patients) showed a pooled mean difference of -0.12°C (95% LOA -0.89°C to 0.65°C) in adults and -0.26°C (95% LOA -0.97°C to 0.46°C) in children. Despite the wide limits of agreement, over 50% of adult ICUs reported using axillary thermometers as the primary mode of temperature measurement in critical illness [Niven 2013b].

1.4.4.2 Temperature based thresholds for fever

As temperature varies according to time of day, sex, race and possibly age, what is febrile for one individual may be normal for another. Different studies have used different thresholds ranging from 37.8°C to 38.5°C [Niven 2013b]. In Niven's meta-analysis comparing peripheral versus central thermometers, 37.8°C was the most commonly used threshold for fever [Niven 2015], whereas 38.2°C was the median as stated by clinicians in the EUROBACT survey [Niven 2013]. The effect of the device is also important as evident from Niven's meta-

analysis: in the fever range (considered to be temperatures $\geq 38.0^{\circ}\text{C}$) the pooled mean difference was -0.008°C (95% LOA -1.44°C to 1.46°C) in adults and -0.53°C (95% LOA -1.49°C to 0.43°C) in children. The sensitivity of peripheral thermometers in detecting centrally defined fever was 64% (95% CI 55-72%) and specificity of 96% (95% CI 93-97%) [Niven 2015]. For pragmatic purposes, the UK National Institute of Health and Care Excellence uses Wunderlich's threshold of $\geq 38^{\circ}\text{C}$ as a fever grade temperature in their guideline for the initial assessment and management of feverish illness in children under 5 years of age, irrespective of device and site of measurement [NICE 2013]. For the following analyses in this thesis I have adopted this definition of fever.

1.5 Fever in the intensive care unit

Regardless of the aetiology, all critical illness involves the activation of the immune response. This is underpinned by Polly Matzinger's Danger Hypothesis of immunity – that the immune system does not distinguish between self and non-self, but recognises danger, whether from an external source (e.g. infection) or from within (e.g. trauma) [Matzinger 2002]. It follows, that as fever is a part of the innate immune response, it is likely to be commonly observed in critical illness even in the absence of infection. However, as described above, heat production requires energy. Critical illness is characterised by an imbalance of oxygen consumption and delivery, creating an oxygen debt. Non-essential energy hungry processes would need to be economised to reduce this debt. If fever, as part of the immune response, has been superseded by more sophisticated immune processes or medical treatment, it may be such a non-essential process. Whether a fever response is seen in critical illness therefore depends on whether (a) there is a central regulator that can 'switch off' the febrile response as a redundant process, and (b) the benefit fever may or may not confer is outweighed by the energy that may be needed to generate it.

Rats, injected with lipopolysaccharide, can enter a hypometabolic and hypothermic state, even prior to a fall in cardiac output and oxygen delivery and the appearance of hypoxia (measured as the ratio between NAD⁺/NADH ratios). The fall in metabolic activity can in part be mitigated by a concurrent fluid bolus. This suggests that adaptive mechanisms may try and prevent a subsequent oxygen debt in rats, but not so if there are adequate reserves that would allow an increase in oxygen delivery [Corrigan 2014].

It may be that fever as part of the immune response cannot be switched off in humans. There is currently no known 'central regulator' that can conditionally switch off physiological processes based on energy reserves. However, the existence of such a regulator is proposed by the Central Governor hypothesis [Humphrey 2015]. According to the hypothesis, energy hungry defence mechanisms such as the immune response may not be activated when the cost of such as response would lead to a worse state. For example, a full-blown immune response may not be mounted during a famine, when the cost of the immune response may be catastrophic, compared to a more prolonged but self-limiting illness. Neuronal regulation of immunity is well recognised, so such a central governor may exist. Alternatively, the benefits of fever may outweigh the risks, or rather the physiological costs. This may be particularly so if other immune mechanisms are inadequate against the pathological threat or there are no curative treatments – for example, following a viral infection (Figure 1.7).

In addition, intensive care interventions are likely to exert their own influences on body temperature: ventilator circuits are warmed, and humidified, intravenous fluids are at room temperature, extra-corporeal circuits used in renal replacement therapy and extra-corporeal membrane oxygenation (ECMO) are temperature regulated. The environment is also air-conditioned. Therefore, whether fever occurs in the intensive care unit or not is an interplay between the body's ability (and possibly need to) generate a fever and the environmental effects of the intensive care unit in controlling it.

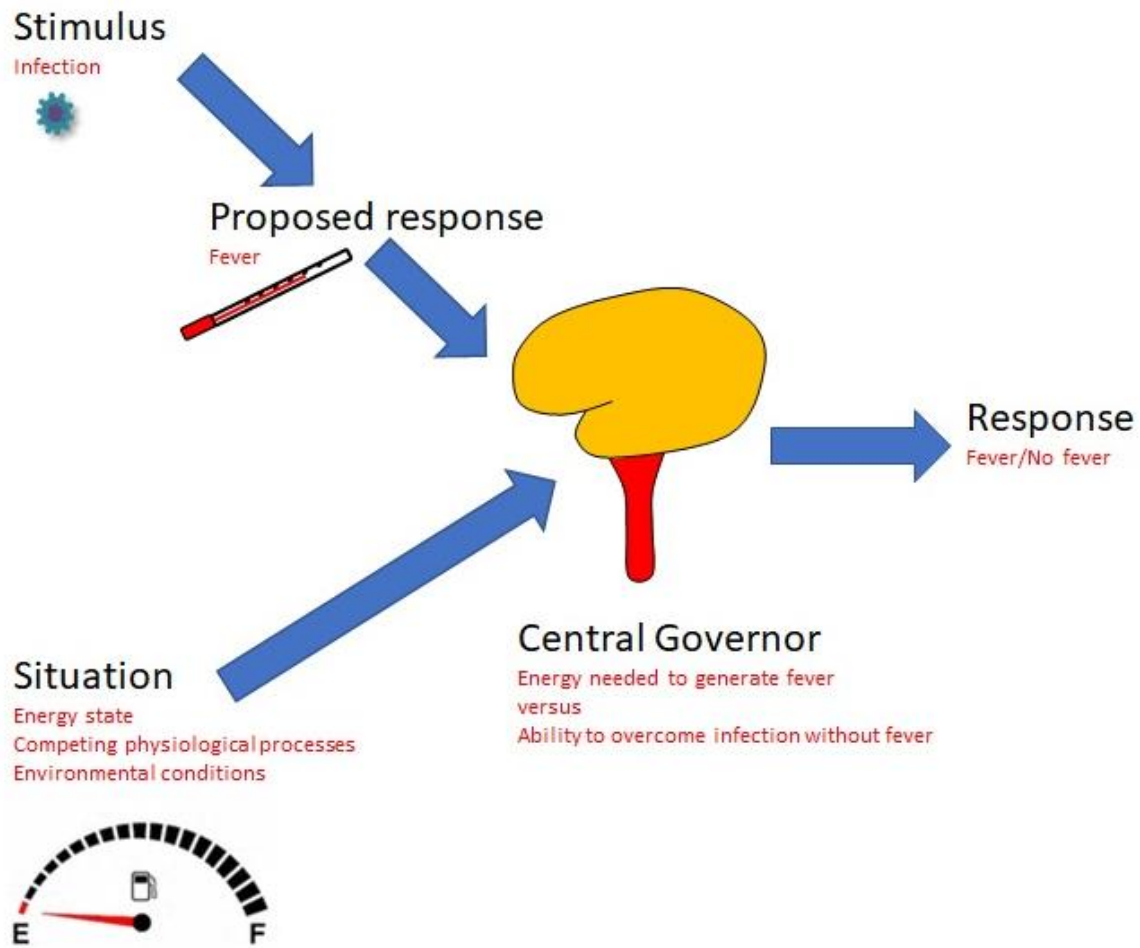


Figure 1.7: The Central Governor hypothesis. The body has set responses to stimuli, such as fever as a response to an invading pathogen. However, the response may not be affordable depending on the overall situation the organism is subjected to: the energy state, the environmental conditions and competing physiological demands. The Central Governor must decide whether the response is necessary and affordable: for example, during a famine, a cold could be allowed to drag on, given that it is likely to be overcome regardless of the immune response; when food is available, then a full blown immune response is mounted, including a fever. Such a Central Governor has been demonstrated for some physiological processes, such as cardiovascular responses to anticipated exercise.

In this following section, I will explore what is known about the epidemiology of fever in the intensive care and the treatment used to control or prevent fever. This will look to establish

whether fever does occur on an intensive care unit, when and in whom it occurs, and the interventions and thresholds used to treat it. This will help us evaluate if fever can have an effect on critical illness, permitted either by the patient's intrinsic physiological regulation or the intensive care interventions the patient is subjected to.

1.5.1 The epidemiology of fever in the intensive care unit

The epidemiology of fever in the ICU has recently garnered interest. Circiumaru and colleagues prospectively observed 100 consecutive admissions in adult ICU over a 4-month period. Seventy episodes of fever (70%) were identified (with a threshold temperature of 38.3°C for defining fever). Most episodes of fever occurred on the day of admission (61/70, 87%); no patient developed a new fever developed after day 6 of admission. Prolonged fever, defined as occurring for >5 days was seen in 16 patients. In their cohort 37/70 (53%) episodes of fever were ascribed to infection, with 9 cases of associated bacteraemia. Patients with fever were more likely to have a longer ICU stay (3.0 days v 2.5 days, p-value 0.04) but there was no difference in mortality (26/70 with fever died, while 8/30 of those without fever died; p-value 0.38) [Circiumaru 1999].

A much larger, regional, retrospective observational study demonstrated a lower incidence of fever in a mixed critically ill population. Laupland et al undertook a database study of 24204 adult ICU admissions over a seven-year period. Fever was defined as a temperature $\geq 38.3^{\circ}\text{C}$. In addition, 'high fever' was defined as a temperature $\geq 39.5^{\circ}\text{C}$. The cumulative incidence of fever was 44% (10730/24204 admissions), with 1932/24204 patients developing a high fever. Of those with fever, 5753/10730 (53.6%) developed it within the first day of admission. Those who did not develop fever on the first day, did so a median of 1.8 (IQR 1.4-3.2) days after admission. The authors also described incidence density of fever i.e. number of days with a fever divided by the number of total ICU admission days: the incidence density for fever was 24.3 per 100 ICU days in their cohort. Prolonged fever (>5

days) was observed in 1976/10730 (18%) of patients. The cause of fever was deemed infective (defined solely by culture positive for an infectious agent) in 1847 (17%) patients. Curiously, 594, i.e. 9% of patients were bacteraemic, same as the Circiumaru cohort. There was no association between ICU mortality and fever. [Laupland 2008].

Diringer et al retrospectively reviewed the associations between temperature and outcomes in a neurological ICU. Defining fever as low (37.5-38.4°C), moderate (38.5-39.0°C) and high (>39.0°C) in 4295 patients, they demonstrated a fever incidence of 70%, and increased mortality, ICU stay and hospital stay in patients with fever. Outcomes were worse according to the degree of fever [Diringer 2004].

Young et al undertook a more selective prospective observational study of ICU patients admitted with infection who had fever, excluding those with neurological injury or within 72 hours of surgery. Fever was defined as the presence of a temperature $\geq 38^{\circ}\text{C}$. Only 51/565 (9%) of the admitted patients fulfilled the inclusion and exclusion criteria. Fever occurred in the first 48 hours of admission, with the mean peak temperature and proportion of patients with a temperature $\geq 38^{\circ}\text{C}$ decreasing over the first 3 days of admission. Mortality was higher in the 51 (16%) patients compared to the remainder (7%) [Young 2011].

Similar epidemiological studies in children are rare. Gordijn and colleagues prospectively observed 202 children admitted to the PICU over a 6-month period. Fever was described as a core temperature $\geq 38^{\circ}\text{C}$ occurred in 82 children (40.6%). In 76/82 children (92.6%) fever developed within the first 48 hours of admission, with infection being the most common cause (41/76). Six patients developed their first fever after 48 hours of their admission; in addition, 8 children developed a second febrile episode after being afebrile for 48 hours. In most of these later febrile episodes nosocomial infections were the cause. Fever in this cohort was associated with a longer ICU stay and need for mechanical ventilation [Gordijn 2009].

1.5.2 The epidemiology of fever treatment in the intensive care unit

The treatment of fever in adult ICU is variable. Niven et al surveyed participating sites of the EUROBACT study, a multi-national observational study of hospital acquired bacterial infections, regarding fever management. Participants from 139 centres responded from 23 countries. The respondents reported the use of 14 different temperature thresholds to define fever, ranging from 37.0°C to 40.0°C, with a median of 38.2°C. Axillary, tympanic and bladder thermometry were most commonly used primary modes of temperature measurements. Thirty-one sites had a formal written protocol for fever management. The prevailing practice was to control the temperature (81% responding 'Always' or 'Most of the time'). Temperature control was more likely to be undertaken in those with neurological injury or shock [Niven 2013].

Pharmacological treatments: Paracetamol was the most commonly used treatment: 64% of respondents (n=139) reported use 'most of the time' or 'always' to treat fever [Niven 2013b].

In a point prevalence study from 38 Australian and New Zealand ICUs, paracetamol was used in just under half the patients. The main indication for use was to alleviate pain and discomfort. The indication of paracetamol use was fever in 9.8%, in addition to 18.2% in whom the indication was pain and fever. The mean temperature at which paracetamol was used for fever was 38.3°C [Hammond 2013].

In Young et al's smaller, prospective observational study, paracetamol was used in up to 70% of patients admitted with infection and fever (excluding those with neurological injury). However, the use of paracetamol was not always temporally associated with fever [Young 2011].

Fewer data are available about the use of non-steroidal anti-inflammatory drugs (NSAIDs) for fever in ICU. Only 9% of respondents in the EUROBACT survey reported the use of

NSAIDs to treat fever 'most of the time', while none of them reported using NSAIDs 'always'. Young reported the use of aspirin (12/51) or steroids (15/51) in a quarter of the patients in his prospective observational study, although given the wide-ranging indications for the use of both drugs, no conclusions can be drawn on the reason for their use [Young 2011].

Similar data do not exist for children in ICU. A recent survey of UK paediatric intensive care unit (PICU) staff, revealed that most staff would treat a temperature $\geq 38^{\circ}\text{C}$, with junior staff and nurses having a lower threshold to treat temperature compared to more senior staff and doctors [Brick 2017].

While paracetamol is widely used in ICU, the effect of paracetamol on temperature in ICU may not be large. In the recent HEAT trial [Young 2015], comparing paracetamol with placebo for fever management in ICU, the temperature separation between the arms was modest. The mean daily peak body temperature was slightly lower in the paracetamol group ($38.4 \pm 1.0^{\circ}\text{C}$ vs $38.6 \pm 0.8^{\circ}\text{C}$) and a lower mean daily average body temperature ($37.0 \pm 0.6^{\circ}\text{C}$ vs $37.3 \pm 0.6^{\circ}\text{C}$).

This had been shown previously by Greenburg and colleagues [Greenburg 2010]. In a retrospective study of patients on ICU with SIRS, they showed that paracetamol reduced temperature in febrile patients (temperature $\geq 38^{\circ}\text{C}$) by 0.86°C . In contrast, those who did not receive paracetamol had a fall in temperature by 0.56°C . Although the difference in temperature decrease between paracetamol treated and untreated fevers was statistically significant, the clinical significance may be questionable.

Two subsequent randomised controlled trials have demonstrated the anti-pyretic effects of paracetamol against placebo. Tsaganos et al studied the effect of paracetamol on temperatures in hospitalised (non-ICU) patients. After 6 hours of treating patients with a temperature $\geq 38.5^{\circ}\text{C}$, 15/39 (38.5%) patients in the placebo achieved defervescence (temperature $\leq 37.1^{\circ}\text{C}$), compared to 33/41 (80.5%) in the paracetamol group [Tsaganos 2017]. Schell-Chaple and colleagues randomised 40 febrile (temperature $\geq 38.3^{\circ}\text{C}$) ICU

patients to receive paracetamol or placebo. The mean decrease in temperature 4-hours post study drug administration was 0.47°C greater in the paracetamol arm compared to the placebo arm [Schell-Chaple 2017]. A randomised controlled trial in patients admitted following traumatic brain injury demonstrated no difference in temperature between patients who received regular 4-hourly paracetamol for 72 hours and those who received 0.9% sodium chloride placebo (mean difference in temperature -0.3°C, 95% CI -0.6 to 0.0°C in favour of paracetamol, p-value =0.09) [Saxena 2015b]. A recent meta-analysis of these data suggested a pooled estimate of temperature reduction by 0.38°C (0.13-0.63°C) [Drewry 2017].

There are no paediatric ICU trials exploring the effect of paracetamol against placebo on temperature. Several trials explore the comparative effects of anti-pyretic agents including paracetamol in non-ICU settings. The mean reported temperature reduction from paracetamol in these studies is between 1.1-1.9°C [Senel 2012; Kokki 2010; Duhamel 2007; Wong 2001]. In a retrospective analysis of anti-pyretics used in PICU, Moffett and colleagues found ibuprofen to be most superior in achieving resolution of fever (defervescence) compared to enteral, rectal and intravenous paracetamol [Moffett 2019].

Physical cooling: Physical cooling aims to increase heat loss through conduction, convection and evaporation. Unlike pharmacological anti-pyretics, physical cooling does not influence the thermoregulatory set-point. Theoretically physical cooling can increase metabolic activity if applied during fever, as the body tries to counteract the surface cooling to maintain the fever range temperature. This can occur through peripheral vasoconstriction and shivering. In order to reduce vasoconstriction some authors suggest warming the peripheries rather than cooling, in order to reduce peripheral vasoconstriction, and increase heat loss [Mackowiak 1998]. Shivering can be mitigated using deep sedation and /or neuro-muscular blockade [Polderman 2009].

The use of tepid sponging to decrease temperature in fever can be traced back to the ancient Greeks but appears in the scientific literature for the treatment of enteric fever by the

British Army in India [Welch 1884]. Although tepid sponging does not compare favourably to paracetamol in terms of reducing temperature (0.55-0.75°C with sponging cf 0.9-1.85°C with paracetamol), it can have an additive effect when used with paracetamol (1.3-1.7°C with paracetamol and sponging cf 0.9-1.3°C with paracetamol alone) [Watts 2003; Meremikwu 2003]. A recent small-scale trial did show that while tepid sponging with paracetamol may reduce body temperature faster, the overall extent of temperature reduction was the same in paracetamol only and paracetamol and sponging arms after 2 hours [Thomas 2009]. However, sponging does lead to reports of discomfort and shivering [Watts 2003; Meremikwu 2003; Thomas 2009].

Fan therapy is used to increase convective heat loss. The effect has been poorly studied [Meremikwu 2003]. In the ICU environment, ice packs, cooling blankets and intravenous cooling are all used to regulate temperature. Many surface cooling devices can target a specific temperature with servo control. The rate of cooling varies, with most surface cooling devices quoting a rate of 1.0-1.5°C per hour, and intravenous cooling systems 2.0-4.5°C per hour [Polderman 2009]. Physical cooling was reported to be used to control temperature in febrile patients 'most of the time' by 26% of the respondents in the EUROBACT study, and 'always' by 9% of the respondents [Niven 2013]. Young reported the use of physical cooling at least once in 12% patients to reduce temperature in fever in his three-centre observational study [Young 2011].

The epidemiological evidence raises two questions:

(1) Fever occurs commonly in the intensive care unit. This means that either fever cannot be reliably switched off by the body, or that the benefits of fever outweigh the physiological cost needed to generate it. The immune benefits of fever have been described above, although most of the work is from *in vitro* or animal models, and not in critical illness. If the immune benefits are intact in critical illness, what are the physiological costs? Critical illness is

characterised by an imbalance of oxygen consumption and delivery. Therefore, to understand the effect of fever on critical illness it is important to understand what effects fever may have on oxygen consumption and delivery.

(2) Fever is treated by clinicians, primarily using drugs that work by resetting the temperature threshold. If fever does have physiological effects, it is important to know whether the treatment of fever reduces these effects. This will help us understand whether fever should be treated.

In the following sections I explore the existing knowledge about the physiological effects of fever and its treatment on oxygen consumption and delivery. I will describe the known effects of fever on oxygen and energy consumption, primarily measured through calorimetry. I will describe the effects of fever on heart rate, stroke volume and vascular resistance, in addition to the effects on the bedside measured composite, blood pressure. For both consumption and delivery, I will describe the known effects of treatment of fever. Given that paracetamol is the most commonly used anti-pyretic, I will focus on the effects of this. However, a lot of the knowledge about oxygen consumption in fever is gained through observations following physical cooling in fever, so I will also detail these experiments.

1.6 Potential cost of fever and its treatment

Hyperthermia can cause protein degeneration, leading to direct cell damage and death. This can lead to loss of gastrointestinal tract integrity, decrease in glomerular filtration rate, liver dysfunction, myocardial damage and arrhythmias, brain injury and lowering of the seizure threshold [Walter 2016]. These deleterious effects occur especially at high grade temperatures.

Several strands of evidence point to the deleterious effect of fever on neurological injury. In critical illness with a neurological focus, such as trauma, post cardiac arrest, stroke and subarachnoid haemorrhage, fever in the first 24 hours is associated with poorer outcome

[Natale 2000; Badjatia 2009; Bohman 2014]. Large-scale epidemiological data suggest that fever following ICU admission is associated with a survival benefit [Young 2012]; however, this was not observed in the sub-group with non-infective neurological disease [Saxena 2015a]. In trials of therapeutic hypothermia following cardiac arrest, those in which the control arm included febrile subjects showed benefits of therapeutic hypothermia, whereas those in which the control arm was maintained at normothermia, there was no benefit from further cooling [Bernard 2002; Nielsen 2013]. The same may also be true of neonatal hypothermia trials post-hypoxic ischaemic encephalopathy trials: in the TOBY trial, in which neonates with hypoxic ischaemic encephalopathy were cooled for 72 hours, there were no survival benefit seen between the cooled and control arms. On secondary analysis, there was evidence of lower rates of children with cerebral palsy at 18 months in the therapeutic hypothermia arm. However, temperatures exceeded 38°C in children in the control arm – this may in part contribute to poorer neurological outcomes in the control arm [Azzopardi 2009].

Fever can reduce the seizure threshold. This association was first studied in animals in the 19th century: Welch found that rabbits had seizures if their body temperature was raised rapidly above a critical point (found to be 44°C), although most died post-convulsion [Welch 1888 L2]. This of greater concern in the developing brain: Wegman showed that the risk of temperature related seizures was much higher in young kittens compared to adult cats. [Wegman 1934]. Epidemiological data confirm the propensity of children to have seizures with an acute febrile illness, with an incidence between 2-14% [Shinnar 2003; Verity 1991; ILEA 1993]. Febrile convulsions rarely occur after the age of 6 years [Livingston 1947, Offringa 2017]. Genetic susceptibility to febrile seizures has been recognised through twin studies, with multiple foci implicated, including genes involved in the immune response linked with febrile illnesses (e.g. IL-1 β) and those involved in neuronal excitability (SCN1A, SCN1B, GABRG2) [Sagazadeh 2014].

Stopping the progression of neurological injury is a focus of intensive care in a significant proportion of patients – at least 10% of all children admitted to UK paediatric intensive care units present with primary neurological disease, but a proportion of patients post trauma and cardiac arrest may also have neurological injury [PICANET 2018]. However, balancing oxygen consumption and delivery is a more fundamental objective in all patients needing intensive care. For the remainder of this thesis I will concentrate specifically on the effect of fever and its treatment on this.

Oxygen consumption and delivery are interdependent. The rate of blood flow (oxygen delivery) to each tissue is controlled precisely according to the need of the tissue. Cardiac output is controlled by the sum of all the local tissue flows [Hall 2011]. Therefore, oxygen delivery depends on oxygen consumption. If oxygen delivery is limited, then beyond a critical point, oxygen consumption and therefore tissue metabolism also falls. This is the hallmark of shock. Once delivery is restored, oxygen consumption increases, although uncertainties remain about point at which delivery dependent consumption ceases – this may vary according to the state of shock, resuscitation and cellular injury, but is also subject to several errors in estimation [Squarrra 2004; Vincent 2004; Tosoni 2016]. It is important to quantify therefore how much oxygen consumption increases by to generate a fever, and also the described effects of oxygen delivery during a fever. If oxygen delivery is unable to match consumption due to critical illness, cellular hypoxia may develop.

1.6.1 The effect of fever and its treatment on oxygen consumption

One of the justifications for treating fever in the intensive care unit is to limit oxygen (and therefore energy) consumption. This attempts to redress the potential mismatch between oxygen consumption and delivery during critical illness. Central to this paradigm are two assumptions: that fever is a redundant immune process, and fever increases oxygen

consumption. In the following section, I will explore the basis for the latter assumption. Some of the quantification of oxygen consumption in critical illness is based on the decrease in oxygen consumption following external cooling in fever. Therefore, the effect of both fever and the treatment of fever, on oxygen consumption are presented together.

The rise in temperature in fever has been associated with energy consumption since Lavoisier showed that animal heat was generated by oxidative combustion of fuel. The army surgeon Francis Welch, in his description of enteric fever, suggested that 'pyrexia...is invariably accompanied by waste of tissue and vital force' [Welch 1884]. This was demonstrated empirically in animals, with oxygen consumption increasing by up to 55% above baseline [Welch 1888 L1]. The ability to measure energy consumption in humans was limited until the invention of calorimetry for human use in the early 1900s [Riche 1915]. Direct calorimetry relies on the principle that heat production in an individual is directly proportional to their energy expenditure. Heat production can be measured as heat released within an adiabatic chamber (i.e. a chamber from which heat cannot escape to the outside environment). Alongside this oxygen consumption and carbon dioxide production was measured, correlating this to energy expenditure (indirect calorimetry) – this allowed for a more time-responsive system for measurement of energy expenditure, for example, in states of exercise [Kenny 2017] (Figure 1.8). Energy expenditure was estimated from measures of oxygen consumed ($\dot{V}O_2$) and carbon dioxide produced ($\dot{V}CO_2$). The process of estimation of energy expenditure is simplified by the Weir equation [Weir 1949]. This uses a series of assumptions, particularly about the ratios in which carbohydrates, fats and proteins are metabolised, to produce the following equation to estimate energy expenditure:

$$\text{Energy expenditure (kCal/day)} = 1.44 \times \{(3.94 \times \dot{V}O_2) + (1.11 \times \dot{V}CO_2)\}$$

Barr and DuBois made the first measurements of oxygen consumption and heat production in humans during malarial fever [Barr 1918], as part of a series of experiments measuring human metabolic activity in different contexts. In doing so they divided the 'malarial paroxysm' into 6 periods: (a) a basal period before the 'chill', (b) a prodromal phase just

before the 'chill', (c) the chill, characterised by shivering (d) a period of rising temperature after the shivering stopped, (e) a period of high continuous temperature, and (f) a period of decreasing temperature. To study the changes in oxygen consumption and heat production in more detail according to these periods, Barr et al repeated these experiments in patients injected with foreign proteins (proteose and typhoid vaccine) to treat rheumatological disease (mostly post-gonococcal reactive arthritis) [Barr 1922]. The findings were very similar to that seen in malaria, with analogous stages. Put together, Barr and colleagues summarised the following:

- (i) During the 'chill' period, there was a sudden increase in heat production, quantified to be a 75-200% rise from baseline. The heat production increased with shivering.
- (ii) This corresponded with an increase in the respiratory quotient (RQ), indicating use of glycogen stores to fuel this rise in heat production
- (iii) There is no rise in heat released during the 'chill' period. This facilitates a rise in temperature
- (iv) Following the 'chill' period the temperature stabilises when there is an equilibrium between heat production and elimination (both elevated)
- (v) During the fall in temperature, heat elimination increases and heat production decreases back to baseline
- (vi) Water vaporisation from the skin and lungs is proportional to the amount of heat eliminated

Altschule and colleagues replicated Barr, Cecil and DuBois' experiments in patients who underwent typhoid vaccine injection for the therapeutic induction of fever [Altschule 1945a]. In addition to measuring oxygen consumption, Altschule measured detailed haemodynamic variables to understand the balance between oxygen delivery and consumption. The authors found that oxygen consumption increased with a rise in rectal temperature, approximately by 7% above baseline per °F rise in temperature (equivalent to 12.5% per °C rise in

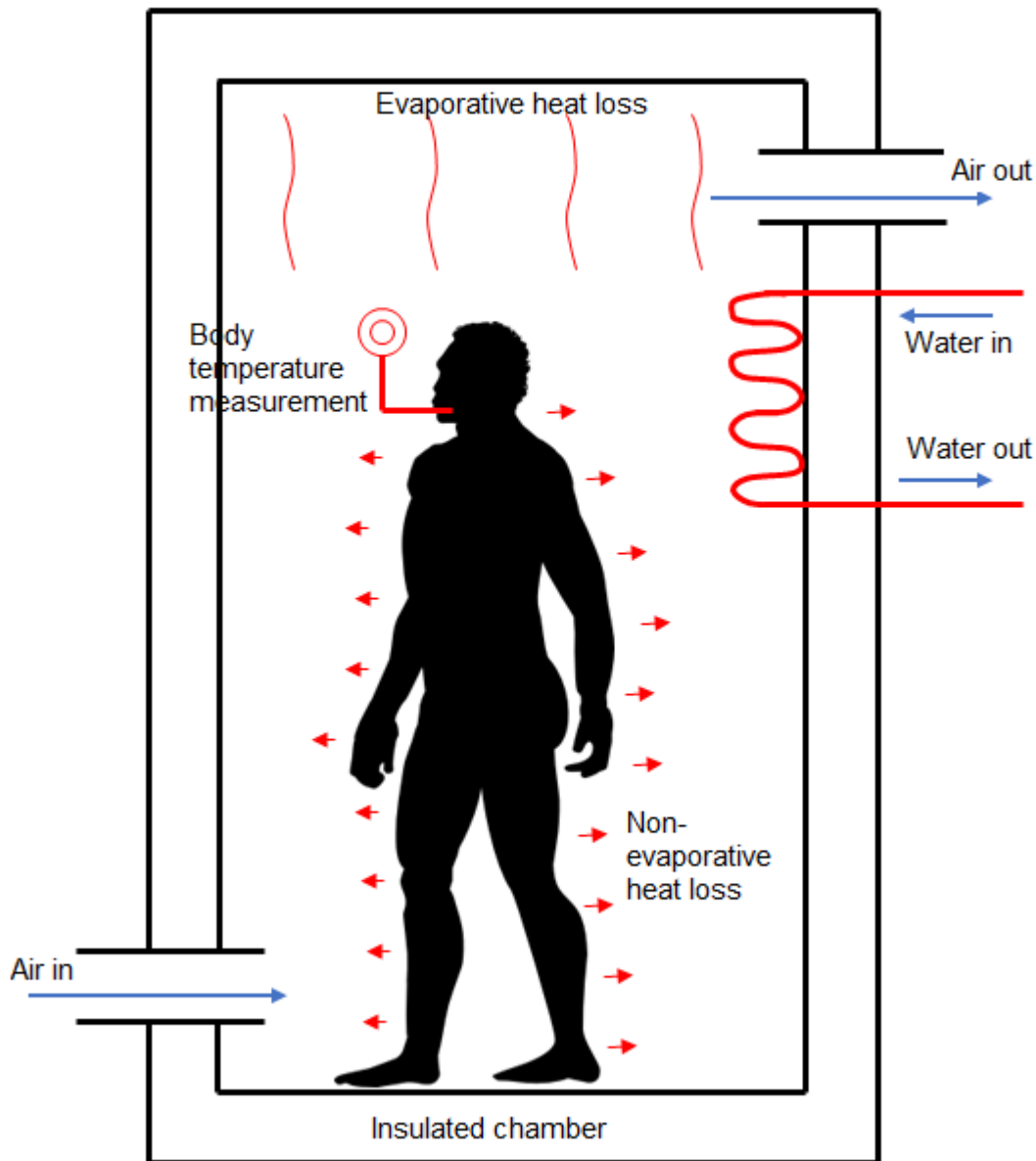


Figure 1.8: Schematic of the Atwater-Rosa direct calorimeter, used by DuBois and colleagues. The subject was placed in the insulated chamber. The non-evaporative heat loss is estimated by the change in temperature of water in the heat exchanger coil. The evaporative heat loss is estimated by measuring the water difference in the water content between the air leaving the chamber and the air entering the chamber (the air leaving the chamber is circulated through a series of cooling chambers to condense water). The oxygen consumed and carbon dioxide produced within the chamber by the subject was also measured, along with the changes in body temperature. The change in oxygen and carbon dioxide is used for indirect calorimetry, correlating it with the heat produced/lost. (Adapted from Heymsfield SB, Bourgeois B, Thomas DM. Assessment of human energy exchange: historical overview. *Eur J Clin Nutr.* 2017 Mar;71(3):294-300.)

temperature). In contrast, the change in cardiac output was more variable between patients at different periods of the febrile response. Shapiro and Stoner demonstrated an increase in oxygen consumption in two healthy men who underwent passive heating by sitting in a bath heated to 42°C [Shapiro 1966]. The increase in oxygen consumption was less than that described by Barr and Altschule (7% above baseline per °C of temperature – almost half of that described by Altschule). The authors did not acknowledge the difference between fever and passive heating – that temperature rise in fever is due to an increase in the temperature set-point, as recognised by Barr and colleagues. The increase in oxygen consumption may be due to the body's thermoregulatory mechanisms to counter the temperature rise, or an effect of a passive increase in the metabolic rate. However, Shapiro and Stoner did question whether bacterial toxins may affect mitochondrial respiratory chain enzymes, increasing the heat production per ml/min of oxygen consumed: thereby inadvertently proposing the process of mitochondrial uncoupling (this may be dysfunctional or adaptive in order to generate a fever).

Several authors undertook measurements of oxygen consumption before and after states of induced hypothermia during cardiopulmonary bypass. Harris et al demonstrated a decrease in oxygen consumption by 15% in patients on cardiopulmonary bypass following cooling to 30°C [Harris 1971]. Seelye et al described a similar doubling of oxygen consumption during the rewarming phase of weaning (increasing temperature between 5-10°C) off cardiopulmonary bypass in children [Seelye 1971].

However, hypothermia during cardiopulmonary bypass provides a poor model for critically ill children with fever: patients have a normal temperature set-point rather than an increased temperature set-point in fever; they are anaesthetised and paralysed; and have a pre-determined cardiac output in the form of bypass flow. Hypothermia decreases the kinetics of physiological processes – increases in oxygen consumption on rewarming possibly reflect the reversal of this process. Manthous et al measured oxygen consumption and energy expenditure in adults on the intensive care unit with fever who were surface cooled to

normothermia for temperature control [Manthous 1995]. All but one of their 12 patients were paralysed and sedated. Oxygen delivery decreased in all 12 patients, from a mean of 359 ml/min to 295 ml/min (17.8%) as the mean temperature decreased from 39.4°C to 37.0°C. Energy expenditure decreased, from a mean of 2481 kCal to 1990 kCal. The respiratory quotient (RQ) changed variably – increasing in 5 and decreasing in 7 patients with cooling. On average, oxygen consumption decreased by 9.7%/°C fall in temperature. In the patient who was not paralysed, oxygen consumption increased as the patient started shivering when cooled from 38.6°C to 37.9°C. This fits with the theory that in fever the temperature set-point is increased, with the body trying to maintain the higher temperature despite surface cooling. Once paralysed thereafter, the oxygen consumption decreased. This would suggest that non-shivering thermogenesis was suppressed in this (and the other 11) patients. It is difficult to know whether this is an effect of illness severity, patient phenotype or any other treatment provided, such as beta-blockers or sedation. Crucially, they had all received paracetamol, although the authors do not state how long before cooling started. It is possible that the decrease in oxygen consumption with cooling coincided with paracetamol reducing the temperature set-point.

Hata demonstrated a similar effect in patients with traumatic brain injury [Hata 2008]. Patients were cooled to achieve normothermia without paralysis. They were observed closely for shivering, with protocolised prevention of shivering using hand warming, face warming and meperidine (an opioid) injection. Those who did not shiver showed a predictable decrease in oxygen consumption by 13%/°C. In those who did shiver there was no mean change in oxygen consumption despite a decrease in temperature. During periods of active shivering, oxygen consumption was observed to increase.

A similar relationship between temperature and energy expenditure in traumatic brain injured patients who were not therapeutically cooled has been described [Bruder 1998]. Energy expenditure and temperature could be modulated using sedatives and paralysis.

The above studies all demonstrate the impact of either blunting the thermoregulatory mechanisms of the body using paralysis or sedation with or without surface cooling. External cooling without modulating thermoregulation in fever theoretically should increase energy expenditure, as the body tries to increase temperature to the higher set-point. This is seen in the instances when thermoregulation is not adequately blunted, for example, in patients who shiver. What happens when the set point itself is targeted? Gozzoli et al in their randomised trial of comparing the effect of metamizol, propacetamol and surface cooling, also used indirect calorimetry to measure oxygen consumption [Gozzoli 2004]. The temperature decrease was similar for all three modes of antipyresis. While oxygen consumption decreased with metamizol and propacetamol, it increased with surface cooling by 10%. Notably, the authors did not use neuromuscular blockade thereby allowing shivering thermogenesis (although all patients were sedated with morphine and midazolam).

McIntyre and Hull examined the effects of fever on energy expenditure using indirect calorimetry in 12 febrile infants on a paediatric ward [McIntyre 1996]. They measured energy expenditure of infants soon after admission to the ward with a febrile illness. Measurements were taken from a ventilated acrylic hood covering the infants' head. Measurements were then taken prior to discharge from hospital after recovery from illness once afebrile. Overall, there was no consistent pattern in the changes in energy expenditure – eight infants had greater energy expenditure while febrile, but four infants had lower energy expenditure when febrile. There was no pattern according to aetiology.

In an analysis of cytokine levels and metabolic rate in critically ill children, Briassoulis et al found that the predominant metabolic pattern in acute critical illness in children was that of hypometabolism, during which energy expenditure did not correlate with levels of IL-6 and IL-10, both fever-inducing cytokines [Briassoulis 2010]. Children admitted to hospital with over 40% burns had an increase in energy expenditure with fever by up to 30% of baseline [Gore 2003]. These children were likely to have more unregulated surface heat loss due to

skin barrier compromise, but equally were likely to be hypermetabolic following their initial injury, widely reported following burns.

1.6.2 The effect of fever on oxygen delivery

Tissue oxygen delivery is determined by 4 physiological variables, in accordance to the following equation

$$DO_2 = [(Hb \times SO_2 \times 1.39) + (PaO_2 \times 0.0031)] \times CO$$

where,

DO₂: tissue oxygen delivery

Hb: haemoglobin concentration

SO₂: haemoglobin oxygen saturation

PaO₂: partial pressure of arterial oxygen

CO: cardiac output, the product of heart rate and stroke volume

While haemoglobin concentration does not vary with temperature, the structure of haemoglobin does, which changes the affinity for oxygen. This translates to a right shift in the oxygen dissociation curve: at high temperatures haemoglobin is more likely to unload oxygen to the tissues. Theoretically, this may benefit tissue oxygenation in shock. In practice, this depends on several factors, including the time of red cell transit through tissue beds as Barcroft and King point out [Barcroft 1909]. Conversely, in the context of alveolar hypoxia, fever may be detrimental as haemoglobin is less likely to be oxygen saturated. A small single centre study of neurosurgical patients describes this [Asgar 2014].

PaO₂ has a relatively small contribution to the oxygen delivery equation, independent of its interaction with haemoglobin (as only a small proportion of oxygen is carried in solution in blood). However, temperature does affect PaO₂: an increase in temperature increases the oxygen tension in blood in vitro [Bradley 1956]. This seems to be reflected by an improved PaO₂/FiO₂ ratio with fever in a pig model of sepsis [Su 2005].

The biggest effect of temperature is likely to be on cardiac output. Cardiac output is the product of heart rate and stroke volume. I will explore the effect of fever (and temperature more generally) on both. However, fever also involves changes in vasomotor tone to conserve heat. Changes in vascular resistance are likely to affect stroke volume by changing afterload. While the effect of fever on vascular resistance is difficult to measure, the effect may be evident through changes in blood pressure, the product of vascular resistance and cardiac output. Changes in blood pressure with fever affects organ perfusion pressure, which in turn determines tissue oxygenation. Also, importantly, blood pressure and heart rate are routinely monitored in all intensive care patients by the bedside and guide treatment. Therefore, the effect of fever on both need to be understood.

1.6.2.1 Effect of fever on heart rate

A direct relationship between heart rate and temperature was demonstrated during the very early descriptions of cardiac contractions in isolated frog heart preparations by William Gaskell. Gaskell found that heating the atria of the heart caused an increase in the rate of atrial and ventricular conduction; heating the ventricle in isolation did not have such an effect. Conversely, cooling the atria slowed the heart preparation down [Gaskell 1882].

Lyon described the *in vivo* relationship between temperature and heart rate by studying a heterogenous group of patients with febrile illnesses, mostly either pneumonia or rheumatic fever [Lyon 1927]. He found that the heart rate increased by 9.13 beats per minute for each 1°F rise in body temperature (equivalent to 16.6 beats per minute for a 1°C rise in

temperature). However, the effect was variable: a high degree of correlation was seen in 44/59 of his patients, but the correlation was particularly poor in the patients who subsequently died from pneumonia.

Tanner described an increase in heart rate between 8-11 beats per minute for each 1°F rise in temperature. Importantly, Tanner described variation both between individuals and within individuals. He postulated that the inter-individual difference could be explained by differences in reactivity of the sino-atrial node to temperature [Tanner 1951]. Whiting, studying a large cohort of prison inmates with higher baseline heart rates, described a lower increase in heart rate for each degree of temperature rise (heart rate increased by 6 beats/min for each 1°F rise in temperature) than described by others [Whiting 1915], suggesting that the temperature-heart rate relationship may be altered by a person's basal metabolic state.

Tanner quantified temperature to account for just over 30% of heart rate variability. He concluded that temperature was the 'most important single factor' accounting for inter-individual variability in heart rate [Tanner 1951]. More recently, Mackowiak, in his reappraisal of Wunderlich's work on normal body temperature, described an increase of heart rate by 4.4 beats per minutes for every 1°C of temperature over the range between 35.6-38.2°C, a much smaller increase than described previously [Mackowiak 1992]. A heart rate increase between 8-17 beats/min for each 1°C rise in temperature has been described in adults with fever [Karjalainen 1986; Weinberg 1989].

Hanna and Greenes characterised the effect of fever on heart rate in infants presenting to the emergency department [Hanna 2004]. Children less than 2 months of age showed poor correlation between heart rate and temperature; children between 2 and 12 months showed a positive correlation between heart rate and temperature. The mean increase in heart rate for every 1°C increase in temperature was 9.6 beats/min. No attempt was made to explore the differences in the temperature heart rate relationship for each child (i.e. within child differences) – each child had only a single temperature heart rate measurement. This, given

the relatively small sample size (n=490), was a limitation of the study. The authors also excluded children who were crying or restless, and those who were dehydrated or hypovolaemic. Davies et al undertook a similar observational study of 21033 children attending the emergency department but excluded those admitted to the hospital as inpatients (thereby omitting possible shocked patients). They found that the heart rate increased by 10 beats/min for every °C rise in temperature [Davies 2009]. Given that much of the utility in understanding the temperature heart rate relationship in the emergency room is in understanding how much of the heart rate increase can be attributed to temperature in children who are potentially shocked, this remains an unanswered question.

Most studies treat the temperature and heart rate relationship as a linear one. This is an assumption, but also Tanner's assertion to be the case (although not evident from the data presented in Tanner in his 1951 paper). Thompson and colleagues described the temperature heart rate relationship as centiles (50th, 75th, 90th and 97th) of heart rate for a continuous range of temperatures. They recorded temperatures in over 2000 children presenting with minor illnesses to general practice. Although close to being linear, the temperature heart rate relationship plateaued at higher temperatures, especially in younger children. The greatest increase in heart rate occurred between 37.0 and 38.0°C in these children [Thompson 2009].

There are no descriptions of heart rate increase in critically ill children with fever. This may be different to that in healthy children, given the metabolic demands posed by critical illness and intensive care. In neonates therapeutically cooled following hypoxic ischaemic encephalopathy, there is a fall in heart rate during cooling and an increase in heart rate following rewarming. Gebauer et al describe a median heart rate increase by 19 beats/min during passive re-warming from 33 to 37°C over 3-7 hours [Gebauer 2006]. Adults studies in ICU demonstrate an increase in heart rate, in the range of 5-7 beats/min for each 1°C [Kiekkas 2007, Asgar Pour 2014]. Haupt reported a mean decrease in heart rate from 111 to 94 beats/min during fever defervescence in ICU [Haupt 1981]. The mean change in

temperature in this cohort was from 101.4°F (38.6°C) to 99.2°F (37.3°C) – a change of 2.2°F or 1.3°C i.e. heart rate decreased by 13 beats/min for each 1°C fall in temperature. The described changes in heart rate for the different populations are summarised in Table 1.1.

Whilst the sinus heart rate increases with temperature, the propensity for tachy-arrhythmias is also increased due to changes in cardiac conduction [Beaulnes 1957]. This is particularly important in children predisposed to cardiac arrhythmias (for example children admitted post-cardiac surgery). As tachy-arrhythmias may cause haemodynamic instability and potentially can be life-threatening, the threshold for prevention/treatment of fever may be lower for those with the existing predisposition for tachy-arrhythmias.

Study	Heart rate increase per 1°C temperature rise (beats/min)	Population
Lyon 1927	16.6	Adults with fever
Whiting 1915	10.9	Prisoners
Tanner 1951	14.5 (oral); 20 (rectal)	Healthy adults
Karjalainen 1986	8.5	Adults with fever
Weinberg 1989	17.3	Adults with fever
Mackowiak 1992	4.4	Healthy adults
Haupt 1981	13	Adults in intensive care unit
Kiekkas 2007	5.2	Adults in intensive care unit with fever
Asgar Pour 2014	7.5	Adults in intensive care unit with fever
Hanna 2004	9.6	Children in emergency department
Davies 2009	10.5	Children in emergency department
Thompson 2009	13.7	Children with fever in GP surgeries
Gebauer 2006	3	Neonates during re-warming following therapeutic hypothermia

Table 1.1: Descriptions of heart rate increase per 1°C rise in temperature in different populations. Where differences have been reported per 1°F rise in temperature, the increase heart rate has been converted multiplying by 1.8.

1.6.2.2 Effect of fever on stroke volume

The effect of fever on stroke volume has not been extensively studied. However, the effect of temperature on stroke volume in heat stress has been well studied. Isolated heart preparations from rats devoid of extracardiac influences show no change in contraction force over a temperature range between 27°C to 37°C, although contractility decreased above temperatures of 40°C [Moore 1966]. *In vivo*, increases in temperature above 40°C by infusing warmed blood in dogs produce a depression in left ventricular ejection [Cooper 1962].

Tanner described no relationship between temperature and stroke volume measurements in a series of young men who had stroke volume measured using ballistocardiography (body surface vibrations measured as a surrogate marker of the ballistic forces of the heart) [Tanner 1949]. However, none of the subjects had a fever – the recorded temperatures ranged between 36.3-37.2°C.

Rowell and colleagues described the effect of heat stress on cardiac output during rest. [Rowell 1964, Rowell 1969]. Temperature was controlled using a heated water perfused garment, from a comfortable temperature (ranging from 33-36°C) to 47.5°C, a temperature previously determined to be the maximum that did not cause pain. Haemodynamic variables were measured using indocyanine green dilution. Raising central blood temperature from 36.5°C to 38.8°C, increased the cardiac output, primarily due to a rise in heart rate, but also an initial rise in stroke volume, followed by a decrease to baseline. As temperature was decreased, stroke volume and cardiac output increased, especially so in one subject, where the temperature was lowered enough to induce shivering (indicating an increase in cardiac output in response to metabolic demand) [Rowell 1969].

Crandall described an increase in left ventricular ejection fraction by 13% following passive heating of healthy male subjects at rest [Crandall 2008]. Central temperature in these subjects was increased from 36.9°C to 38.2°C. This may be an intrinsic response of the human cardiac muscle to heat, or a response to heat induced oxygen consumption. When the change in oxygen consumption was measured by analysing inspired and expired oxygen

fractions, only a small proportion of the change in cardiac output was found to be associated with an increase in oxygen consumption following heating [Rowell 1969].

The relationship between body temperature and stroke volume during the metabolic demand of exercise in heat stress are more complex. Cardiac output and stroke volume both decrease in heat stress during exercise [Rowell 1964]. This was more pronounced at higher workloads. During exercise blood is diverted to skeletal muscles to preserve oxygen delivery to tissues with the highest metabolic demand. With increases in body temperature there is diversion of blood to cutaneous blood vessels. Blood flow is also diverted from the kidneys during exercise and heat stress. While glomerular filtration rate can be maintained during moderate exercise despite a decrease in renal blood flow, glomerular filtration rate decreases in higher ambient temperatures [Radigan 1949]. This fall in glomerular filtration rate may be adaptive to maintain the circulating blood volume. Rowell described similar decreases in hepatic blood flow during exercise and heat stress [Rowell 1965]. It is not known whether there is a critical threshold beyond which the need to maintain global cardiac output and tissue perfusion is prioritised over thermoregulation, for example when a tissue oxygen deficit develops [Rowell 1964].

Heart rate and stroke volume are dependent on each other. Trinity et al used beta blockers to maintain a relatively constant heart rate in subjects during exercise in hyperthermic conditions. Stroke volume increased, especially towards the final 20 minutes of a 60-minute exercise routine [Trinity 1985]. This may suggest that the increase in heart rate may decrease stroke volume during hyperthermia, by reducing cardiac filling time. This is not a linear relationship: cardiac contractility and stroke volume increase with heart rate in response to the intrinsic force-frequency relationship of cardiac muscle (the Bowditch effect) [Bowditch 1871]. The relationship between heart rate, stroke volume and cardiac output is therefore likely to form an optimisation function as shown in Figure 1.9.

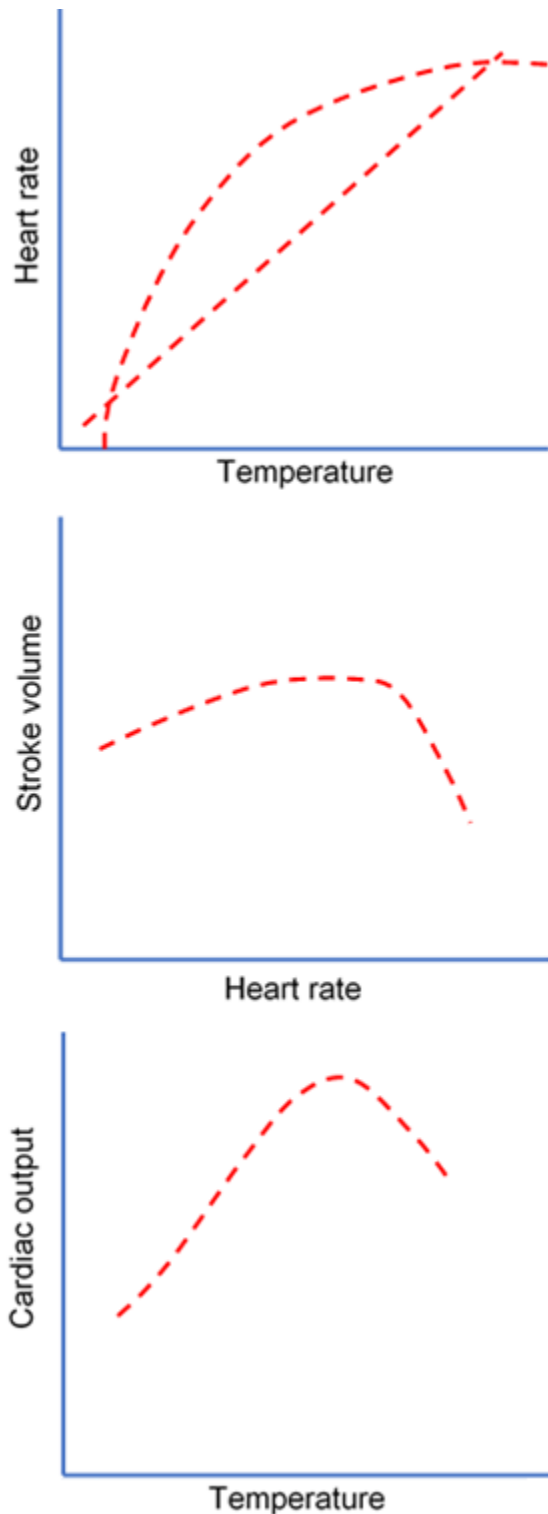


Figure 1.9: Relationship between temperature and heart rate, and potential effects on stroke volume and cardiac output. Heart rate increases with temperature. Although mostly modelled as a linear increase, some evidence to suggest the relationship is non-linear (top).

Stroke volume may increase with heart rate to a degree due to the Bowditch effect (force-frequency relationship of the cardiac muscle) (middle). However, as the heart rate rises further the diastolic time decreases, compromising filling time for the ventricles. This will decrease stroke volume.

Cardiac output is a product of stroke volume and heart rate – as heart rate increases, cardiac output will linearly increase until the point when stroke volume decreases (bottom). If stroke volume increases with temperature before filling is limited by heart rate, then cardiac output could increase exponentially with temperature, rather than linearly.

While the haemodynamic effects of heat stress have been well studied, there are two key differences between heat stress and fever. (1) Heat stress caused by environmental increases in temperature leads to peripheral vasodilation to encourage heat loss and maintain normal body temperature. In fever, peripheral vasoconstriction occurs to conserve

heat and increase the body temperature. (2) In critical illness states such as sepsis, cytokines can depress myocardial activity and lead to a decrease in systemic vascular resistance [Stein 1996]. Haupt et al describe an increase in stroke volume following the decrease in temperature during fever defervescence (100°F or 37.8°C used as a cut-off). They also demonstrated an increase in left ventricular stroke work index with the decrease in temperature. This led them to conclude that fever is associated with a decrease in stroke volume and left ventricular contractility [Haupt 1981]. However, their subjects demonstrated an increase in heart rate and decrease in blood pressure with fever. As the change in heart rate and blood pressure change the filling time and afterload for the left ventricle, the conclusion that fever causes a decrease in cardiac contractility does not follow. Weinberg demonstrated that indices of left ventricular contractility did not change with fever, even though stroke volume decreased, and heart rate increased with fever. The authors concluded that the changes in stroke volume relate to heart rate and preload [Weinberg 1989]. Cardiac output did not significantly change in either study, with large variability between patients.

Although changes in stroke volume and cardiac output with fever have not been reported in children, in neonates being cooled for hypoxic ischaemic encephalopathy, heart rate, stroke volume and cardiac output increase during re-warming. Cardiac output increases from a median of 169 ml/kg/min at 33°C to 254 ml/kg/min at 37°C [Gebauer 2006].

1.6.2.3 Effect of fever on vascular resistance

The effect of temperature on vascular resistance is important in the interpretation of cardiac output changes. External heat is likely to lead to vasodilation of skin vessels to maintain body temperature by losing heat through radiation; in fever blood flow to the skin surface is restricted to prevent heat loss. Weinberg measured blood flow to the finger, forearm and toes using strain gauge venous occlusion plethysmography and laser Doppler flow

measurements. Briefly, strain gauge venous occlusion plethysmography involves inflating a cuff proximally to the area of interest. The rationale is that with venous outflow occluded, any change in volume will be proportional to continued arterial inflow. Weinberg did not find any difference between blood flow to the forearm or the middle finger in subjects when febrile and following recovery from their febrile illness. Blood flow however did increase with temperature when subjects were externally heated around their trunk. Weinberg also examined changes in blood flow to the toes when the subjects were lying down and then when they lowered their legs, using laser Doppler flowmetry. In fever, there was a reduction in blood flow to toes when the leg was lowered; this was not seen when the subjects were externally heated. These results suggest that while blood flow to the skin may increase during external heating, vasoconstriction may not be evident when febrile compared to when not [Weinberg 1989]. In contrast, Boyle demonstrated an increase in skin blood flow measured by laser Doppler flowmetry associated with defervescence following the use of paracetamol [Boyle 2010].

Most estimations of systemic vascular resistance are derived from measurements of blood pressure (arterial – venous) and cardiac output. Whether the systemic vascular resistance is affected by fever may depend on the contribution of the resistance from skin blood vessels that constrict during fever to increase temperature on systemic vascular resistance. Theoretically at least, in children the contribution of peripheral vascular resistance to systemic vascular resistance will be relatively high compared to adults, due to a higher body surface to weight ratio.

Critical illness states such as sepsis have their own effects on vascular resistance. These can be variable, especially in children, where cold and warm shock can present [Brierley 2008; Deep 2013]. The mediators of vasogenic changes in sepsis are similar to those of fever – cytokines such as IL-1 and TNF- α , with prostaglandin as a downstream mediator [Burgdorff 2018]. It is unknown whether the effects of fever and those of the critical illness states compete, and if so, which one predominates – children with warm shock for example

still develop fever. Studies in rats suggest distinct pre-ganglionic mechanisms control sympathetic pathways involved in the prostaglandin induced brown adipose tissue thermogenesis and baroreceptor driven vasogenic responses [Tanaka 2013]. This would allow fever to develop independently of vasogenic changes in states of circulatory shock seen in critical illness. While splanchnic vasoconstriction responds mostly to changes in arterial blood pressure via baroreceptors, thermogenesis and vasodilation in brown adipose tissue were responsive to injection of intra-cerebroventricular prostaglandin injections [Morrison 2001].

1.6.2.4 Effect of fever on blood pressure

Clinically, blood pressure is measured as a composite of systemic vascular resistance and cardiac output. Blood pressure is regulated by central baroreceptor reflexes, rather than cardiac output or changes in arteriolar resistance changes in individual tissue beds [Hall 2011]. However, blood pressure is commonly used as a target for therapeutic interventions and therefore it is important to understand the effects of fever on blood pressure.

Blood pressure has consistently been reported to drop following exogenous heat stress [Rowell 1969; Trinity 1985; Crandall 2008], secondary to peripheral vasodilation to facilitate heat loss. However, in fever, the opposite should occur given that peripheral vasculature (i.e. skin) should constrict to prevent heat loss and raise the body temperature. Many of the early descriptions of blood pressure changes with fever did not distinguish between fever and septic shock [Weinberg 1989]. Haupt took care in describing changes according to different cohorts in ICU – those with fever (temperature $>37.8^{\circ}\text{C}$) with and without infection, and those with and without coronary artery disease. In their cohort of 36 patients, mean arterial pressure increased from 83 (mean) \pm 2 (standard deviation) mmHg with fever, to 90 ± 3 mmHg following fever defervescence (thereby suggesting blood pressure decreases during fever). The differences in mean arterial pressure remained statistically significant in patients

with bacterial infection and those without. However statistical significance was not seen in the 12 patients with coronary heart disease (79+/-3 with fever vs 86+/-3 mmHg without), suggesting the blood pressure changes may be secondary to a decrease in cardiac output with fever.

More recent studies in adults admitted to ICU have tried to describe the effect of fever on blood pressure in general, surgical and neurosurgical ICU patients. Kiekkas et al described a statistically significant decrease in mean arterial pressure from 82.7+/-13.6 mmHg pre-fever to 80.0+/-13.6 mmHg during the height of fever: the authors recognised this as being of little clinical significance. The change in mean arterial pressure was greatest in patients who had a peak temperature $\geq 39^{\circ}\text{C}$ [Kiekkas 2007].

Celik et al found a statistically significant decrease in systolic blood pressure during fever (temperature $\geq 38.3^{\circ}\text{C}$) in 46 patients in a surgical ICU, from 125 mmHg to 118.5 mmHg, decreasing further to 115.5 mmHg 2 hours after onset of fever. The mean and diastolic blood pressures also decreased, although this did not reach statistical significance (mean blood pressure fell from 84.5 mmHg to 82 mmHg during fever and 79.8 mmHg 2 hours post) [Celik 2011]. Asgar Pour et al described a similar statistically significant decrease in systolic blood pressure in 35 neurosurgical patients with fever, but no significant decrease in mean and diastolic blood pressures [Asgar Pour 2014].

The haemodynamic changes with fever therefore are complex. From the evidence available it can be summarised as the following (Figure 1.10)

- Heart rate rises with fever, although the degree of rise may vary according to several variables
- Stroke volume may increase with temperature up to a point, but decreases in fever, due to the complex interplay of heart rate and vascular resistance. Metabolic demand may also alter this relationship.

- Cardiac output measurements have not been shown to be different during and after fever. However, reported results suggest a large degree of variability, with increase in some subjects and decrease in others.
- Systemic vascular resistance changes are likely to depend on the relative effects of vasoconstriction of skin vessels to preserve heat – while this may be low in adults, it may be higher in children with a higher surface area to weight ratio.
- Blood pressure decreases with fever, although not to a clinically significant degree.

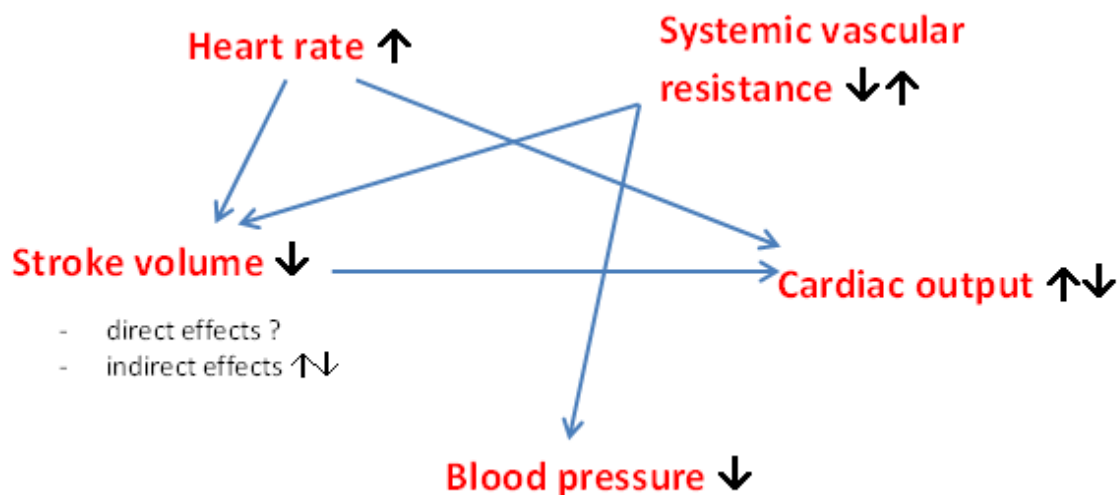


Figure 1.10: Effects of fever on haemodynamic parameters and the interactions between measured and unmeasured variables. Heart rate increases during fever, although there is unlikely to be a linear relationship between temperature and heart rate. Fever may have a variable effect on systemic vascular resistance, depending on the relative contribution of the peripheral (skin) vascular resistance to the systemic vascular resistance. Fever may have a direct effect on stroke volume, but this has not been adequately demonstrated. Stroke volume may increase with heart rate up to a point and then decrease. Stroke volume may decrease if the systemic vascular resistance is high. Cardiac output is a product of heart rate and fever – there is no significant change in cardiac output with fever, although a wide variability is described. Blood pressure, a product of systemic vascular resistance and cardiac output, has been described to fall with fever.

1.6.3 The haemodynamic effects of the treatment of fever

While the haemodynamic effects of fever have been studied in detail, it is important to establish whether treating fever reverses these effects. Paracetamol is most commonly used to treat fever, even in the intensive care unit. Paracetamol works as an anti-pyretic by inhibiting the action of prostaglandin on the hypothalamus [Mirrashekian 2018] thereby resets the temperature set-point. This should therefore reverse all the haemodynamic effects seen with fever, although paracetamol could have specific effects e.g. intravenous paracetamol preparations contain mannitol, which can have haemodynamic effects independent of the anti-pyretic action. External cooling works by directly cooling the body surface. As the temperature set-point is unaffected, peripheral (skin) vasoconstriction should occur to preserve heat. This can have specific effects on the systemic vascular resistance and blood pressure.

1.6.3.1 The haemodynamic effects of paracetamol

The haemodynamic effects of paracetamol were initially observed through case reports and small, retrospective observational studies. Although initial reports were thought to be anaphylaxis reactions, Brown described repeated episodes of transient hypotension, requiring adjustment of vasopressors in two patients in ICU [Brown 1996]. Mackenzie et al described a median fall in mean arterial blood pressure to 89% of baseline in 53 patients, with just over a quarter needing fluid to restore blood pressure [Mackenzie 2000].

Following these reports, prospective observational studies in various settings demonstrated largely consistent results. Several authors described a significant drop in blood pressure within 15 minutes of administration of paracetamol in critically ill patients, with peak effect reported around 45-60 minutes [Boyle 1997; Boyle 2010; Krajcova 2013; Mrozek 2009; Hersch 2008; de Maat 2010; Picetti 2014; Cantais 2016]. The effects size varied between 7-44%, with most authors reporting a 10-15% drop in blood pressure from baseline (mostly

mean and systolic). However, not every administration resulted in a fall in blood pressure, and most report 16-46% of episodes of drop in blood pressure requiring an adjustment in treatment (either fluid or titration of vasoconstrictor doses). Mrozek described a greater fall in blood pressure in those needing neurocritical care with a mixed ICU cohort. Picetti observed a systolic blood pressure drop by 11.3% and a mean blood pressure drop by 9.7% 2-hours post paracetamol dose in a 32-patient cohort of ICU patients receiving neurocritical care: 46.9% of these episodes required an increase in vasoconstrictor doses. This effect was mostly seen and studied in patients with fever, although was not confined to febrile patients alone. Contrary to this, Poblete found no significant change in blood pressure with propacetamol, a pro-drug of paracetamol, over a 1-hour observation period [Poblete 1997]

Schell-Chaple et al undertook a randomised controlled trial of paracetamol versus placebo to evaluate the temperature and haemodynamic effects of paracetamol over a 4-hour period in critically ill patients. All patients were febrile with a temperature $>38.3^{\circ}\text{C}$. Patients were either administered intravenous paracetamol or 0.9% sodium chloride placebo, and no other thermoregulatory treatments were permitted. There was a significant drop in time-weighted average values for temperature (by 0.47°C , 95% CI 0.18-0.76 with paracetamol), systolic blood pressure (17 mmHg, 95% CI 8-25 mmHg), mean blood pressure (7 mmHg, 95% CI 1-12 mmHg) and heart rate (6 beats/min, 95% 1-10 beats/min). The peak effect on temperature and haemodynamic values occurred 2-hours post paracetamol [Schell-Chaple 2017].

The mechanism behind the blood pressure changes seen post paracetamol dose has not been clearly delineated. The hypothesis is that paracetamol releases the thermoregulatory peripheral vasoconstriction in fever, thereby causing the blood pressure to fall. This may also hold in cases where paracetamol is used as an analgesic – the release of pain related vasoconstriction. Krajcova et al used pulse contour analysis in two patients to demonstrate whether the fall in blood pressure was due to a fall in cardiac output, systemic vascular resistance or both. They found that the fall in blood pressure was associated with a variety of

haemodynamic changes - a fall in cardiac output, systemic vascular resistance and a combination of the two. When data were pooled, there was no statistically significant difference in cardiac output or systemic vascular resistance from baseline post paracetamol. [Krajcova 2012]. Boyle et al instead used laser Doppler flowmetry to assess cutaneous vascular conductance. Following paracetamol, skin blood flow and cutaneous vascular conductance increased in febrile patients, with no change in afebrile patients, therefore supporting the hypothesis that paracetamol releases peripheral vasoconstriction [Boyle 2010].

An alternative explanation for the fall in blood pressure post paracetamol is the osmotic diuretic effect of mannitol used as a stabilising agent in most intravenous paracetamol formulations. Chiam et al conducted a blinded triple crossover trial in 24 healthy adult volunteers with intravenous paracetamol, mannitol and 0.9% sodium chloride. Paracetamol caused the greatest and statistically, if not clinically, significant decrease in blood pressure – systolic blood pressure dropped by 0.54 mmHg (95% CI -0.6, 1.7 mmHg) and mean blood pressure by 1.85 mmHg (95% CI 1.1, 2.6 mmHg). The effect was transient. This was associated with a decrease in systemic vascular resistance, with a compensatory increase in cardiac index. Mannitol was not associated with any significant haemodynamic changes. There was a small decrease in blood pressure associated with 0.9% sodium chloride, although the effect size was lower than that seen with paracetamol [Chiam 2015]. While this trial confirms the haemodynamic changes seen with paracetamol are likely to be in response to the drug itself, the effect size was both modest and transient. The authors only observed for 45 minutes post infusion, even though most observational data describe a peak effect at 45-60 minutes, and Schell-Chaple et al described a peak effect at 2-hours post paracetamol administration. The subjects in this study were all healthy with no fever: it is possible that the effect is more pronounced in critically ill patients as the compensatory increase in cardiac index may not occur following the initial fall in systemic vascular resistance.

Although paracetamol, rather than the mannitol in the intravenous preparation, may be causing the decrease in blood pressure, intravenous preparations seem to have a greater effect than enteral ones. In a randomised trial of intravenous versus enteral paracetamol in 50 critically ill patients, 12 episodes of hypotension occurred following intravenous paracetamol compared to 4 episodes following enteral paracetamol (16/197 (8.2%) doses in total). Eleven of the 16 hypotensive episodes required clinical intervention. The different pharmacokinetic profiles of intravenous and enteral administrations were accounted for by measuring plasma paracetamol concentrations – a higher maximum concentration was seen with intravenous administration compared to enteral, even though the total area under the curve within 6 hours of the dose did not vary. It is possible that the differences in incidence of hypotensive episodes relate to the maximum plasma paracetamol level achieved [Kelly 2016].

Whilst most of the studies have been performed in critically ill adults, very few have been performed in critically ill children. Given the proposed mechanism of fall in blood pressure – a fall in the systemic vascular resistance following paracetamol due to the release of thermoregulatory peripheral vasoconstriction – children might show a greater effect given their larger body surface area to weight ratio. Allegaert and Naulaers described the haemodynamic effect of paracetamol in 72 neonates recruited for two pharmacokinetic studies. Mean blood pressure dropped by 3 mmHg 1-hour post dose, although returned to baseline soon after. Systolic and diastolic blood pressures did not change. None of the neonates were febrile. The effect was greater in neonates with a lower baseline blood pressure [Allegaert 2010]. The most convincing evidence for the haemodynamic effect of paracetamol in critically ill children comes from a recent retrospective analysis of blood pressure changes following 777 paracetamol doses in 608 children admitted to a cardiac intensive care unit. Five percent of children had a fall in mean blood pressure by more than 15% and 20% had a fall in mean blood pressure by more than 10%. The peak effect occurred 60 minutes post dose. Fall in blood pressure was independently associated with

younger age and higher blood pressure. In 16% of children with at least a 10% drop in mean blood pressure treatment was given either as a fluid bolus or a vasoactive infusion to increase the blood pressure [Achuff 2019].

1.6.3.2 The haemodynamic effects of external cooling

The haemodynamic effects of external cooling have been studied primarily in the context of therapeutic hypothermia. Cardiac output can decrease between 25-40%, mainly due to a decrease in heart rate, although systemic vascular resistance and arterial blood pressure both rise [Polderman 2009]. However, in the context of fever, these effects may not be as pronounced given that normothermia rather than hypothermia is the target. Gozzoli et al compared the effects of paracetamol, metamizol (an analgesic and anti-pyretic) and surface cooling in febrile critically ill patients (10 in each arm). Compared to paracetamol and metamizole, external cooling increased blood pressure, with the mean blood pressure increasing by 5 mmHg at 4 hours post initiation of external cooling. There was no significant difference in heart rate or stroke volume with external cooling [Gozzoli 2004]. This suggests that systemic vascular resistance increases during external cooling in fever, possibly through further vasoconstriction of surface vessels to reduce heat loss.

Schortgen conducted a randomised controlled trial to assess the effect of external cooling on vasopressor dose in adults with sepsis in fever [Schortgen 2012]. Although the trial did not demonstrate a difference between patients who were cooled or not in the primary endpoint of a reduction in vasopressor dose at 48 hours (detailed below), there was a decrease in vasopressor dose at 12 hours after cooling began. This would be consistent with the hypothesis that cooling is associated with peripheral vasoconstriction, which can improve blood pressure and allow weaning of vasopressors. That this effect did not last may be because fever occurs early in the ICU course. Alternatively, once cooled blood circulates,

the temperature effects on the cardiac output may affect blood pressure, and subsequent vasopressor weaning.

1.6.4 The effect of fever on the balance between oxygen delivery and consumption

Most studies described above investigated the changes in either oxygen consumption or oxygen delivery in fever. Only Altschule et al described changes in both oxygen delivery and consumption in patients post typhoid vaccine [Altschule 1945a]. They divided the effects of fever into the chill phase and the subsequent flush phase. During the chill phase, peripheral vasoconstriction occurred with a rise in oxygen consumption and the respiratory quotient. Cardiac output increased in 3/6 of their cohort, although the cardiac output relative to the oxygen consumption fell by 15%. In the remaining 3/6 patients the cardiac output decreased. In one patient this was as much as 57% relative to the oxygen consumption. In the flush phase cardiac output rose by as much as 182%. This increased more than oxygen consumption (an increase as high as 86% relative to the oxygen consumption). These results suggest that an increase in cardiac output, either primarily or as a secondary gain, occurs as a response to the increase in the oxygen consumption required to develop fever.

Despite this, an ongoing motivation to treat fever in critically ill patients remains. Like most interventions in intensive care units this is to prevent an imbalance between oxygen delivery and consumption (although by the bedside this may translate to maintaining physiological normality). An interesting observation was made in the recent TRACT trial [Maitland 2019] that provides insight into the risks of interventions to boost oxygen delivery during fever. Children with severe anaemia (haemoglobin concentration <60g/L) in sub-Saharan Africa underwent two randomisation steps: to either receive an immediate or a delayed transfusion, and to receive 20ml/kg or 30ml/kg whole blood or equivalent (i.e. 10ml/kg or 15ml/kg packed red cells). In the secondary analysis comparing the latter randomised trial, there was a clear change in risk of mortality between the arms according to temperature at randomisation.

Those who had a temperature less than 37.5°C at randomisation had a significantly lower risk of mortality with 30ml/kg of blood relative to 20ml/kg. The reverse was true for those with a temperature of 37.5°C and above (those who received 20ml/kg had a significantly lower risk of mortality compared to those who received 30ml/kg). Theoretically, increasing the haemoglobin concentration through transfusion increases oxygen carrying capacity and therefore delivery. Therefore, the temperature effect is surprising. Three hypotheses follow (1) fever does not create an oxygen debt from an imbalance between oxygen consumption and delivery; (2) increasing transfusion volume does not increase oxygen delivery to meet any oxygen debt secondary to fever (this may be due to changes in oxygen affinity of transfused blood); or (3) some other effect of transfused blood such as inflammation or reactive oxygen species generation, or a volume effect, may outweigh the benefits blood transfusion may provide in reducing oxygen debt.

All the evidence presented so far points towards the benefits of fever as part of the immune response. Fever may be detrimental in those who are unable to meet the increase in metabolic demand needed to generate fever. Fever is treated, although the treatment of fever also poses some burdens. It is therefore important to understand the clinical effects of fever and its treatment.

1.7 The clinical effects of fever and its treatment

In critical illness, fever may increase the oxygen debt in some cases, where consumption is increased without adequate increases in delivery, leading to hypoxia. This oxygen debt due to fever may be undesirable in critical illness. This is based on the assumption that fever in humans has become an evolutionary relic: a redundant mechanism in the human immune system, rendered even more redundant in the era of antibiotics and modern medicine. Fever has been demonstrated to have a role in the immune response in vitro and in animals. In

critical illness, particularly if infection is the primary cause for the illness, can fever offer some advantage as part of the host response? If so, it would be important to know whether any advantage potentially outweighs any effect that fever may have in the oxygen delivery and consumption mismatch in critical illness.

Delineating the immune outcomes of fever in vivo, particularly in critical illness is difficult. Several immune responses are activated in parallel. Dissociating the effect of fever alone may not be possible. Epidemiological evidence may provide some suggestions towards the role of fever. The effect of treatment of fever, compared to not treating fever, provides the best evidence. The effect may be specific to a treatment, such as pharmacological treatment or physical cooling. This is clinically relevant and will help guide management in the intensive care unit.

In the following section, I will first briefly look at the evidence for fever being of benefit in infectious diseases in the non-critically ill population. I will then concentrate in more detail on what is known about the effect of fever on outcomes in critical illness. This will be based on epidemiological studies of fever in the intensive care unit, and more specifically, randomised controlled trials of fever treatment in critically ill patients.

1.7.1 The clinical effect of fever and its treatment in non-critical illness

Fever is treated commonly in the community by parents with over-the-counter medicines, primarily to reduce temperature [Walsh 2007]. This is based on the popular belief that fever is harmful. Evidence suggests that fever may be beneficial in the early resolution of specific diseases. Compared to children treated with placebo, those with varicella infection treated with paracetamol had a longer time to resolution of illness [Doran 1989]. Use of ibuprofen has been associated with an increase in severe secondary bacterial infection [Mikaeloff 2007; Dubos 2008], and weak association with invasive Group A Streptococcal sepsis [Lesko 2001]. Patients with rhinovirus infection are found to shed rhinovirus for longer when

treated with aspirin and paracetamol, compared to treatment with placebo [Stanley 1975; Graham 1990]. The effect of paracetamol on malaria parasite shedding has been studied in various settings with conflicting results: while initial studies suggested paracetamol use reduced parasite clearance compared to mechanical cooling, subsequent studies did not show this effect of paracetamol when compared to placebo or standard anti-malarial treatment alone [Brandts 1997; Hugosson 2003; Kofoed 2011]. Suppurative complications of pneumonia (empyema and lung abscesses) have been associated with non-steroidal anti-inflammatory drug use [Byington 2002; Francois 2009]. In children with bacterial meningitis, Pelkonen et al have explored the benefits of paracetamol over placebo in a 2x2 randomised controlled trial, with a cefotaxime infusion or boluses as the parallel intervention. There was no demonstrable benefit in paracetamol reducing mortality or neurological sequelae [Pelkonen 2011]. A meta-analysis of a subset of this evidence in children concluded that anti-pyretic treatment did not prolong the time to fever resolution or length of illness [Purssell 2013]. Using an entirely theoretical approach, Earn et al suggest a more novel effect of fever: reduction of disease transmission by limiting inter-personal contact. Using mathematical modelling they suggested that treatment of fever can increase the rate of seasonal influenza infections by 5% [Earn 2014].

Based on this, and a lack of contrary evidence to suggest the benefit of fever treatment, the National Institute of Clinical and Health Excellent (NICE) in the U.K. recommends

‘Do not use antipyretic agents with the sole aim of reducing body temperature in children with fever.’

in their guideline Fever in Under 5s [NICE 2013].

1.7.2 The clinical effect of fever and its treatment in critical illness

Perhaps the effect of fever is best demonstrated in the critical care population. Critical care outcomes such as death or length of stay are clinically significant, objective and easily

measured. Critical illness is characterised by organ system failure and a lack of functional reserve: therefore, any advantage or disadvantage provided by fever, even if otherwise redundant, may be detectable in this population. Early epidemiological studies in adults associated fever with a worse outcome compared to the absence of fever. Circiumaru showed an increase in length of stay for patients who developed a fever (by a mean of 0.5 days) but no difference in mortality [Circiumaru 1999]. Laupland's much larger retrospective observational study did not show any association between mortality and fever, although those with high fever had a higher risk of mortality (20% died if temperature $\geq 39.5^{\circ}\text{C}$ during admission vs 12% in those with a maximum temperature $< 39.5^{\circ}\text{C}$). The association was variable according to diagnostic categories – there was some evidence of increased risk of mortality with fever in medical patients, those post cardiac and non-cardiac surgery, but lower risk of mortality in those with trauma or neurologic injury [Laupland 2008]. These results are contrary to the higher risk of mortality with fever seen from a neurological only ICU, where the degree of fever correlated with increased mortality, ICU and hospital length of stay [Diringer 2004].

Young's small but prospective observational study of those with infection and fever (but excluding those with neurological injury) found that mortality was comparatively higher than all other ICU patients (i.e. ICU patients without infection and fever, or those with neurological injury) [Young 2011]. However, Young et al subsequently produced the most compelling epidemiological evidence for the association of fever with an improved outcome in ICU. In their retrospective observational study of 636,051 admissions to ICU from the UK, Australia and New Zealand, in-hospital mortality was reduced at temperatures in the fever range, relative to the mortality in those with a maximum temperature of $36.5\text{-}36.9^{\circ}\text{C}$ in the first 24 hours of admission. The relationship between fever and reduced mortality was mostly evident in those with infections. The lowest risk of mortality in those with a temperature was between $39.0\text{-}39.4^{\circ}\text{C}$ in the Australia and New Zealand cohort, and $38.0\text{-}38.4^{\circ}\text{C}$ in the UK cohort. In those without infection, the risk of mortality was also reduced in those with fever.

However, the lowest risk of mortality in this cohort was in those with a maximum temperature of 37.5-37.9°C in the first 24 hours of admission [Young 2012]. Further sub-group analysis has suggested that this beneficial effect of fever is not seen in those with non-infective neurological injury such as traumatic brain injury and stroke [Saxena 2015], and also not seen in patients with neutropenic sepsis [Weinkove 2015]. This last piece of evidence leads to the hypothesis that the beneficial effects of fever are potentially mediated through the action of neutrophils, therefore the beneficial effect is an immune-mediated one.

Although the epidemiological evidence is compelling, it is based on maximum temperatures in the first 24 hours of admission only. It is quite possible that those who had fever range temperatures had a lower risk of mortality because they were more likely to be treated with anti-pyretics, and at higher temperatures the risk of the temperature outweighed the benefits conferred by anti-pyretic treatment. Alternatively, those with low temperatures may have had higher a risk of mortality because they were not allowed to (through external cooling or empirical anti-pyretic treatment) reach fever range temperatures. The first 24-hour maximum temperature may also be a surrogate marker of time of presentation in the illness trajectory: those without temperature may be presenting late in the course of illness at which point they have lost the ability to generate heat or thermoregulate. In a more comprehensive Japanese study of a smaller cohort, Lee et al prospectively collected data on daily maximum temperatures and treatment given in ICU. In patients with sepsis, a maximum temperature in ICU between 37.5 and 38.4°C conferred a risk adjusted mortality benefit (compared to 36.5-37.4°C), but the use of NSAIDs and paracetamol independently increased risk adjusted mortality. In non-septic patients, maximum temperatures above 39.5°C increased the risk of mortality, and there was no effect of NSAIDs or paracetamol treatment [Lee 2012].

Contrary to this, in a smaller retrospective propensity score matched analysis by Suzuki et al, ICU patients who received paracetamol had an associated reduction in-hospital mortality risk compared to those who did not. The association was weakened when paracetamol was used for treatment of fever in patients with infection related illnesses [Suzuki 2015]. This

demonstrates the problems with the interpretation of observational data, despite the use of careful prospective data collection to account for confounders, or retrospective techniques such as propensity score matching to reduce bias.

Randomised controlled trials have been attempted in ICU to examine the effect of fever control, especially in the context of infection and sepsis. A small trial of ibuprofen (n=16) versus placebo (n=13) to evaluate the safety and physiological effects of ibuprofen in sepsis showed no difference in mortality [Haupt 1991]. The study did demonstrate a significant decrease in temperature following ibuprofen use compared to placebo, but there were no significant differences in the haemodynamic or biochemical profiles between groups. A larger trial followed, to examine the effect of ibuprofen on survival in sepsis. The trial of 455 patients was powered to detect a relative risk reduction in 30-day mortality from 30 to 19.5%. There was no difference in 30-day mortality, duration of shock or development of ARDS. Even though there was separation in temperature and heart rate between the ibuprofen and placebo groups in this trial, those in the ibuprofen arm had mean temperatures less than 38°C prior to the administration of ibuprofen. Interestingly, the use of paracetamol was not restricted in the trial (as it was not designed to detect the effect of fever, rather the effect of ibuprofen): those in the placebo arm did receive more paracetamol than those in the ibuprofen group [Bernard 1997]. A further trial of intravenous ibuprofen in 120 adults with fever (44% of who were critically ill) showed no difference in mortality or length of stay in 3 dose groups and placebo arms, although the trial was designed to look for a defined decrease in temperature [Morris 2010].

Two small trials were carried out in surgical intensive care patients. The first of these was designed to detect an outcome of a decrease in temperature by 0.5°C 24 hours post intervention (external cooling versus no anti-pyretic use in those with a fever defined as a temperature $\geq 38.5^{\circ}\text{C}$). In this small study of only 18 patients, fever seemed to resolve after 24 hours in both arms, with no difference in length of stay or mortality [Gozzoli 2001]. The second trial was set in a trauma intensive care unit, where patients were randomised on day

3 of their ICU stay to either to an aggressive (paracetamol +/- external cooling at temperature thresholds above 38.5°C) or permissive (paracetamol + external cooling at a threshold above 40°C) strategy of fever control. The trial was stopped after a first planned interim analysis, following 7 deaths in the aggressive arm compared to 1 death in the permissive arm [Schulman 2005].

A similar trial exploring aggressive versus permissive thresholds of fever management in general ICU patients by Niven et al was unable to recruit a projected number of patients and was therefore under-powered. In the 26 patients recruited, there was no difference in their primary outcome of 28-day mortality [Niven 2013].

Two trials sought to study the effect of external cooling in fever control in septic patients. The larger of the two used external cooling in adults on ICU with sepsis and fever (temperature $\geq 38.3^{\circ}\text{C}$) to maintain hypothermia (n=101) versus no cooling (n=99). The primary outcome measure was the decrease of vasopressor dose by 50% at 48 hours post randomisation. Although there was no significant difference in the primary outcome, there was a significant difference in vasopressor dose at 12 hours. There was also a risk-adjusted mortality benefit with cooling at 14 days, but this did not extend to ICU or hospital discharge [Schortgen 2012]. The other trial assigned 65 patients with sepsis and fever (temperature $\geq 38.5^{\circ}\text{C}$) on ICU to either a low temperature range (36.0-37.5°C) or a high range (37.5-38.3°C). Those in the low temperature range group had a higher risk of crude 28-day mortality, with temperature being a significant independent predictor of mortality following regression analysis. However, neither of the target temperature ranges being compared were in the authors' definition of the fever range [Yang 2013]. A trial of therapeutic hypothermia (temperature maintained between 32-34°C for 48 hours) in adults on ICU with bacterial meningitis had to be stopped early (after recruitment of 98 of the intended 276 patients) because of a risk of poor functional outcome at 3 months with the intervention compared to controls exposed to standard care. Standard care did not include targeted temperature

management, although the control cohort had a median temperature of 37°C, with the 75th centile temperature also below 38°C [Mourvillier 2013].

The HEAT trial was the largest trial to test the effect of paracetamol for fever in critical illness. Young et al randomly assigned patients on ICU with suspected infection to either receive paracetamol or placebo in response to fever (temperature $\geq 38^\circ\text{C}$). The study drug was administered 6-hourly until resolution of fever, discontinuation of antibiotics, discharge or death. Rescue external cooling was allowed if the temperature rose above 39.5°C. The primary outcome was ICU free days to day 28 (a composite outcome of death and ICU length of stay). There was no difference between the two arms (paracetamol and placebo) in ICU free days to day 28, nor were there differences in ICU length of stay, death at 28 days or 90 days. However, there was very little separation in temperature between the two arms, with mean daily peak temperature being 38.4 \pm 1.0°C in the paracetamol arm and 38.6 \pm 0.8°C in the placebo arm [Young 2015].

A few small trials, designed to evaluate the differences in biomarkers following the use of anti-pyretics and placebo, did not demonstrate any differences in mortality or length of stay. Honarmand showed no difference in changes in cytokine levels with paracetamol compared to placebo [Honarmand 2012], while Memis described the same with lornoxicam [Memis 2004]. Janz studied the effect of paracetamol as an anti-oxidant in sepsis – while paracetamol appeared to reduce the levels of F-isoprostanes, a marker of oxidative injury, on day 2, this did not translate to lower levels on day 3, the primary outcome of the study [Janz 2015].

The multiple trials, even though they use different anti-pyretics and outcomes, lend themselves to meta-analysis for temperature management strategies. Dallimore et al analysed 15 studies including 13 randomised controlled trials. Active temperature management as defined as the intervention arm in intervention versus placebo trials, or the more restrictive threshold in restrictive versus permissive threshold studies. There was no association between active temperature management and improvement in mortality, ICU

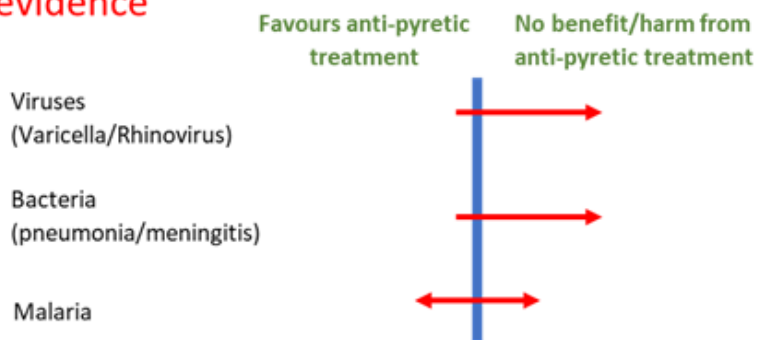
length of stay or hospital length of stay. There was a decrease in temperature seen with active temperature management, by 0.62°C with drug treatments compared controls (95% CI 0.51 to 0.72°C) and by 1.59°C (95% CI 1.35 to 1.82°C) with physical cooling [Dallimore 2018]. A more sophisticated individual patient level analysis of active temperature management from existing trials analysed 1413 trial participants (707 active temperature management, 706 less active temperature management). Once again, no benefit of active temperature management was demonstrated, with a hazard ratio for survival time of 0.91, 95% CI 0.75-1.10 [Young 2019a].

Subsequently Young et al have reported a feasibility trial in 184 patients to formally test active temperature management against usual care in mechanically ventilated ICU patients (the REACTOR trial). The intervention included use of paracetamol 6 hourly, in addition to surface cooling mechanisms to maintain a body temperature between 36.5-37°C. Feasibility was assessed by temperature separation over the first seven days of the intervention. There was a temperature separation of 0.5°C between the two arms (higher in the usual care arm) and this was most evident over the first 48 hours after which fever rarely persisted. There was no significant difference between the secondary outcomes of ICU-free days or survival at 90 days [Young 2019b].

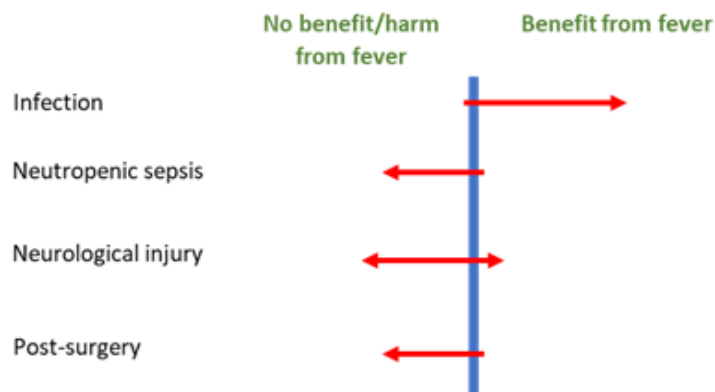
Although epidemiological evidence points to an association between positive outcomes and fever, this has not translated to harm with active management of fever in randomised trials (Figure 1.11). Equally, a benefit in terms of mortality or length of stay with the treatment of fever is not seen. Taken together, the following inferences can all be valid:

- fever confers neither harm nor benefit in critical illness
- the benefit that fever confers is equally counter-acted by the benefits of fever treatment (or vice versa)

Disease specific evidence



Epidemiological evidence in ICU



Trial evidence in ICU

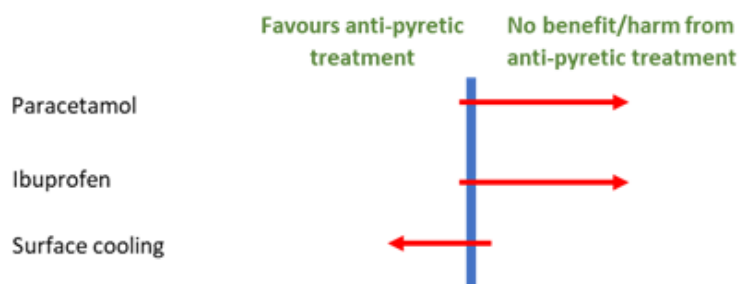


Figure 1.11: Summary of evidence regarding the clinical effects of fever and its treatment in humans. Treatment of fever in viral and bacterial infections has been associated with prolonged and more severe illness; in malaria the evidence is equivocal. Epidemiological studies suggest a benefit of fever in patients admitted to ICU with infection, but not in neutropenic sepsis or post-surgery. Following neurological injury, fever is largely associated with harm, although in one study it was associated with improved survival. However, trial evidence for treatment of fever in ICU suggests that pharmacological treatments do not offer benefit, with a small benefit (in reducing vasoconstrictor dose and mortality at 14 days) with surface cooling.

- any effect of fever or its treatment is too small to have been detected by the best quality evidence available so far

1.8 Aims, objectives and hypothesis

Children are largely missing from the current evidence base. There are several reasons to expect that fever may have a potentially different effect on critically ill children compared to adults:

- a) Children have relatively immature immune systems. Like the controversial theory 'phylogeny recapitulates ontogeny', which states that developmental stages of an organism reflect evolutionary changes of the species, the immune responses in children may reflect those of species from earlier in the evolutionary scale. Therefore, while fever may be redundant in the mature adult immune armoury, it may have a significant role to play early on in life.
- b) Thermoregulatory mechanisms are also immature in children, particularly in infants. Children have a relatively large body surface area to weight ratio compared to adults. This allows for greater surface heat loss. Conversely, relatively more heat may be preserved by reducing surface heat loss during fever. There is a greater proportion of brown adipose tissue in new-borns compared to adults, which may have a unique effect on thermoregulation through mitochondrial proton leak.
- c) The circulatory system develops over childhood. Children have high heart rates compared to adults at rest. The relative contribution of heart rate and stroke volume to the cardiac output changes with age. In children, the predominant pattern of shock in sepsis is one of low cardiac output, partly due to the compensatory haemodynamic mechanisms in children (difficulty in doubling the heart rate from a high baseline). In adults hyperdynamic shock is more prevalent, although it is difficult to dissociate the effects of treatment (and access to it) from inherent differences in pathophysiology.

- d) Energy reserves may be lower in children compared to adults. Febrile responses may increase energy consumption in critical illness, increasing oxygen debt in children beyond levels experienced by adults.
- e) The effects of anti-pyretic treatments may differ between children and adults. Physical cooling may have a greater effect in children given the larger body surface area to weight ratio. Paracetamol is metabolised by the liver: the activity of liver enzymes such as CYP2E involved in metabolising paracetamol increases through childhood to adult levels [Fernandez 2011].
- f) The outcomes of children admitted to the intensive care unit are far better than those in adults. Typically, the mortality rate in paediatric ICU (PICU) in the UK is less than 4%, compared to 25% in adult ICU. The most common primary reason for admission is infection. Viral infections such as bronchiolitis are common causes for admission. There are no curative pharmacological treatments for most viral illnesses, therefore recovery relies on immune function. Fever may have a greater role to play in such circumstances.

Based on this, the aim of my thesis is to determine the impact of fever and its treatment in children admitted to PICU. I will investigate the epidemiology of fever, the use and effectiveness of treatment and the impact of both on oxygen delivery and consumption.

I put forward the following hypothesis:

Null hypothesis: In critically ill children, fever does not impact on critical illness outcomes by significantly affecting the balance between oxygen consumption and oxygen delivery.

Test hypothesis: In critically ill children, fever significantly alters the clinical outcomes of critically ill children admitted to ICU by affecting the balance between oxygen consumption and delivery.

To test the hypothesis, the following questions need answering:

- (1) What is the incidence of fever in children who are admitted to the paediatric intensive care unit? In particular, what is the incidence of fever early in the course of illness (i.e. due to primary reason for admission). This is particularly important as this is likeliest to be the period when oxygen delivery and consumption are least balanced. Early temperature has been associated with mortality in adults. As part of the innate immune response, fever is likely to occur early, and also impact further immune responses.
- (2) What is the incidence of treatment of fever? This is important to understand to design any future randomised controlled trials investigating the treatment of fever. It is also important to understand what the threshold for treatment is. If there is an association between fever and outcome (as shown in adults) is this because they are exposed to the treatment for fever?
- (3) What is the effectiveness of treatment of fever? The treatment may or may not have an effect on temperature reduction – fever may naturally resolve without treatment, which may have other undesired effects. This was highlighted in particular by the modest temperature separation between the two arms in the HEAT and REACTOR trials.
- (4) What is the change in oxygen consumption and energy expenditure with fever in ICU? A common argument for temperature reduction in children in ICU is to prevent unnecessary energy expenditure. Although heat production in fever should require energy, (a) in children heat conservation may contribute relatively more to temperature increase, (b) energy metabolism and body composition changes through childhood development towards adulthood, and (b) the energy required has not been quantified.
- (5) What is the change in cardiac output in response to fever in ICU? While oxygen diffusion and carriage by haemoglobin also determines oxygen delivery, these are

both manipulated on the ICU. Cardiac output is also manipulated, usually is in response to changes in heart rate and blood pressure, without direct measurements of stroke volume. In addition, as paracetamol, the first line treatment of fever has been shown to reduce blood pressure in adults, this is important to investigate in children in terms of the changes that may occur to oxygen delivery with paracetamol.

(6) Is temperature associated with ICU outcomes? Adult epidemiological evidence points to this, even though active fever management has not proved to be beneficial. Also fever may have a more pronounced outcome if the potential immune benefit outweighs the energy cost – is this evident in the comparative effect of fever in different populations?

To answer these questions, I will describe results from the following investigations:

- i. An epidemiological investigation of fever in critically ill children. This will include
 - Profiling of the temperature of children admitted to ICU over the first 48 hours
 - Quantifying the incidence and timing of new incidence of fever on ICU
- ii. An epidemiological investigation of the treatment of fever and the effect this has. This will include
 - Quantifying the incidence of and the threshold for treatment of fever
 - The effect of fever treatment on temperature
- iii. The impact of fever and its treatment on oxygen consumption.
 - Measurement of oxygen consumption and energy expenditure in fever using indirect calorimetry
- iv. The impact of fever and its treatment on oxygen delivery. This will include:
 - The impact of fever on age standardised heart rates for children in the ICU, where several other factors affect heart rate

- The impact of fever and treatment with paracetamol on haemodynamic measures such as stroke volume and cardiac index
- v. The association between temperature and ICU outcomes
- The exploration of the association between early temperature and mortality in PICU
 - A comparison between this association and that in a comparative cohort from sub-Saharan Africa with infection but without the provision of intensive care. This will provide insight into the risk-benefit balance of fever in critical illness with and without intensive care.

Chapter 2: The epidemiology of fever in the paediatric intensive care unit

2. 1 Introduction

In order to establish if fever has any effect on recovery from critical illness in children, it is important to understand how commonly fever occurs in the intensive care unit. Evidence from adult ICU suggests that fever occurs in 40-70% of patients. Fever occurs early in the admission, the incidence diminishing over the first five days. This may be due to fever being part of the early immune response in critical illness. Alternatively, fever is controlled on the ICU leading to its disappearance beyond the first few days of admission: either through thermoregulated ICU interventions, such as temperature control of ventilator circuits, extracorporeal circuits and intravenous fluids, or through antipyretic treatments.

Paediatric epidemiological data are limited to a small, single centre study over 6-months. As with adults, approximately 40% of children developed fever, mostly within the first 48 hours [Gordijn 2011]. Small single-centre studies however can lead to misrepresentative sampling, demonstrated in the adult literature (Circiumaru cf Laupland). Children may have a lower potential to develop a fever in the thermoregulated environment of an ICU, especially given a larger body surface to weight ratio. Anti-pyretics may be used more or less frequently than in adults.

In this chapter, I will describe the epidemiology of fever in children admitted to PICU at Great Ormond Street Hospital, London. I will do this two-ways: retrospectively, using electronic health record data from over 10000 admissions, and prospectively, as part of a national observational study to assess feasibility of a temperature management trial in fever.

2.2 Aims and hypothesis

Aims of the study:

To describe the incidence of fever in the paediatric intensive care unit (general and cardiac ICU) in an unselected population, and more specifically, in those admitted with a confirmed or suspected infection.

Null hypotheses:

The incidence of fever in PICU is comparable to the only reported paediatric incidence of 40%, with fever occurring early during ICU admission

Alternative hypotheses:

The incidence of fever in PICU is considerably different to previously reported in critically ill children

2.3 Methods

This was an epidemiological study to observe the incidence of fever. In order to understand the incidence of fever across all children admitted to PICU, a retrospective review of electronic health records, to understand the temperature distributions of all children admitted was undertaken. However, the association between fever and low mortality has been demonstrated in critically ill adults admitted with an infection. To identify the incidence of fever in this sub-group, a prospective observational study was used, as part of a national multi-modal feasibility study for a proposed temperature threshold trial.

2.3.1 Retrospective study of temperature profiles and incidence of fever:

Study design: This was a retrospective study of the temperature profiles of an unselected population of children admitted to PICU limited to the first 48 hours of their admission.

Setting: This (and all subsequent) work was undertaken at the Great Ormond Street Hospital NHS Foundation Trust's Intensive Care Units. The hospital has the largest critical care facility for children in the UK. There are 3 separate intensive care units: a 17-bedded general paediatric intensive care unit (PICU), an 8-bedded neonatal intensive care unit (NICU) and a 20-bedded cardiac intensive care unit (CICU).

There are 650-700 admissions to PICU each year. Just over 40% of these are planned admissions following surgery: either high risk surgery such as tumour resection or renal transplants, or surgery in high risk patients with chronic health needs. The remainder of admissions are unplanned. Just under half of the emergency admissions are from wards in the hospital, while over half are from local district general hospitals, transported in by the Children's Acute Transport Service (CATS). Approximately 80% of children are mechanically ventilated, with the unit providing advanced ventilator support such as high frequency oscillation and airway pressure release ventilation. Continuous veno-venous haemofiltration is provided as renal support.

NICU admits 250-300 children each year. The unit is primarily a regional surgical unit, with no attached maternity unit. General and neurosurgical patients form a large part of the patient population. The unit is also a quaternary referral unit for assessment of children considered for ECMO and children born with Vein of Galen malformations.

The standardised mortality rate (SMR) for PICU and NICU patients are reported as a single unit by PICANET (the UK Paediatric Intensive Care Audit Network) – this is consistently between 1 and 1.2. The crude mortality rate is between 4 and 5% of all admissions [PICANET 2018].

There are approximately 800 admissions to CICU each year. Just below 80% of these admissions are planned following surgery, 650 of these are post cardiac bypass. This includes children post heart transplant (approx. 25/year) and lung transplant (10/year). CICU also runs a supra-regional ECMO service, with approximately 50-70 cardiac and respiratory ECMO runs each year. The SMR for CICU is between 0.75 and 1.2, with a crude mortality rate of 4% [PICANET 2018].

Population: Data from **all** children admitted to the PICU/neonatal intensive care unit (NICU) and cardiac intensive care unit (CICU) at Great Ormond Street Hospital between 1st April 2012 and 31st December 2017 (68 months) were included. This interval was chosen as the time from when the Electronic Health Record was adopted at Great Ormond Street Hospital till when the data were collected for analysis.

Bias: There is unlikely to be sampling bias as all admissions over a long period of time were considered. Information bias was minimised by using the same data extraction algorithm for the entire population. Missing data due to lack of charting or electronic health record problems could not be minimised. Confounders were not accounted for, although no outcome measure beyond the description of temperature distributions were sought for this study.

Sample size: This was a retrospective study of all ICU admissions over a fixed period, therefore a prior sample size was not calculated.

Data sources and collection: Admissions were identified from data submitted to the Paediatric Intensive Care Audit Network (PICANET), including admission and discharge dates and times. Data were submitted to PICANET for PICU and NICU together as these units are managed by the same medical team, with some interchange of patients between the units. Therefore, for all further analysis PICU and NICU will be treated as a single general PICU.

Temperature and mode of measurement data were collected searching the electronic health records (Philips IntelliSpace Critical Care and Anaesthesia, Philips Electronics, Netherlands) using an SQL query (Appendix A). Hospital numbers for consecutive admissions, as identified from data from PICANET submissions, were used within the search term to avoid inclusion of children not admitted to ICU (the same electronic health record is used for children admitted to the cardiology ward). The search term was also restricted to collect data within the time-period being studied.

Data analysis: Temperature data were initially matched to the mode of temperature measurement in MS Excel (Microsoft Inc., WA, USA) using Visual Basic (VBA). Modes of measurement included the following labels: Axillary, Tympanic, Oesophageal, Rectal, Bladder, Core, Peripheral and Skin. Peripheral, skin and unlabelled temperature measurements were not included for further analysis as peripheral measurements may not reflect central temperature measurements, especially in cases of circulatory shock. Although axillary and tympanic measurements may not be equivalent to core temperature measurements (those labelled Core, Oesophageal, Bladder and Rectal), axillary temperature measurements using Chemical TempaDots (3M, Ontario, CA) are the primary mode of thermometry in Great Ormond Street Hospital. TempaDot measurements estimate temperature within 0.33°C (95% limit of agreement -0.04 to 0.69°C) of a central temperature [Niven 2015], which was judged to be an acceptable margin.

Temperatures were then assigned to hourly intervals relative to the admission date and time for the first 48 hours. If more than one temperature measurement was available for an hour, then the highest temperature recording for that hour was used. All temperature measurements less than 32°C were excluded, as they were likely to either be spuriously recorded or mislabelled peripheral temperatures (e.g. toe temperature for core-toe gap measurement).

Sub-groups were analysed according to unit of admission (cardiac and non-cardiac), type of admission (planned or unplanned) and age-bands (infants <1 year and all children ≥1

year). The distribution of temperatures was thought likely to be different between general and cardiac ICU as most children were admitted to cardiac ICU following planned cardio-pulmonary bypass surgery. These children were less likely to have a fever at admission as many of these children will have been subject to deep hypothermic circulatory arrest in theatre or will have had a regulated low temperature during bypass. Typically, these children develop an inflammatory response 6-12 hours post admission, which may be characterised by a fever. Fever is more aggressively controlled in the cardiac ICU however given the risk of cardiac arrhythmias with fever post bypass. Infections are likely to be suspected a high proportion of children with unplanned admissions, and therefore these children were analysed as a sub-group. Typically, children <1 year of age make up just under half the admissions to PICU. As these children have a higher surface area to weight ratio compared to older children and therefore may lose heat more readily, these children were analysed as a sub-group.

Temperature distributions were described using median and centiles over the 48-hour period. Proportions were calculated with the 95% confidence intervals as:

$$95\% \text{ CI} = p \pm 1.96 \times \sqrt{\frac{p(1-p)}{n}}$$

where p is the proportion, n is the sample size.

Distributions of temperature between sub-groups were compared using the Kolmogorov-Smirnov test. The distribution of the first occurrence of fever by hour was analysed, with the probability by hour calculated and presented as a time-to-event graph. Similarly, the distribution of the final hour of fever was analysed, along with the number of hours each admission had a fever.

Patient consent: Individual patient consent was not sought as this was a case report study involving routinely collected data, with no reporting of patient identifiable data.

2.3.2 Prospective study of temperature profile in those admitted with infection

Study design: To understand the incidence of fever specifically in those admitted with an infection, prospective data were collected as part of the Fever Observational Study. The Fever Observational Study was one part of the NIHR funded Fever Feasibility Study: a multi-modal study into the feasibility of conducting a trial to compare a permissive versus a restrictive temperature threshold for the treatment of fever in children admitted to PICU. The Fever Feasibility Study included a qualitative study of parent and clinician attitudes to fever, an observational study of fever epidemiology and treatment in 22 UK PICUs (the Fever Observational Study) and a 4-centre pilot trial comparing a permissive temperature threshold of 39.5°C versus a restrictive threshold of 37.5°C for fever treatment on PICU.

For the purposes of this thesis, only data submitted from Great Ormond Street Hospital for the Fever Observational Study (as 1 of the 22 participating centres) are used here as these data were primarily collected by the author.

The Fever Observational Study was designed with the Chief Investigator for the Fever Feasibility Study (Prof Mark Peters) and the Clinical Trials Unit, ICNARC (Intensive Care National Audit and Research Centre). The aim of the Fever Observational Study was to

- 1) Estimate the size and define the characteristics and temperature distribution of a potential trial population
- 2) Describe the use of anti-pyretics interventions in UK PICUs in a potential trial population, with a view to identifying a temperature threshold for intervention within standard care
- 3) To estimate the characteristics of selected outcome measures in a potential trial population and facilitate sample size calculation for a trial

In this chapter I will describe the temperature distribution of eligible participants from Great Ormond Street Hospital, across the Paediatric, Neonatal and Cardiac ICUs

Patient population: The population was defined as potential participants for a trial comparing a permissive versus restrictive temperature threshold for the treatment of fever. The eligibility criteria for the trial were as follows:

Inclusion criteria:

- an unplanned admission
- suspected or confirmed infection

Exclusion criteria:

- acute encephalopathy, including convulsive status epilepticus;
- post-cardio-pulmonary bypass;
- known/suspected myocardial disease;
- severe rhabdomyolysis;
- malignant hyperthermia;
- neuroleptic malignant syndrome;
- drug-induced hyperthermia;
- patient receiving palliative care or if death was perceived as imminent

Children with acute neurological impairment were excluded given the evidence of hyperthermia being detrimental in neurological injury. Children post cardiopulmonary bypass and myocardial disease were excluded to prevent potential for tachyarrhythmias. Those with drug induced or malignant hyperthermia and rhabdomyolysis were excluded to prevent exacerbation of rhabdomyolysis. Children who were receiving palliative care or in whom death was imminent were excluded to not withhold analgesic drugs such as paracetamol and NSAIDs.

Bias: Sampling bias was minimised by deciding a priori eligibility criteria. However, by allowing children with suspected infections to be included, an element of observer bias was introduced. It was not known if children whether temperature control mechanisms were used to reduce temperature i.e. whether the child was on regular anti-pyretics or on an extra-

corporeal circuit throughout – this introduces confounder bias. However, the aim of this study was to describe the distribution of daily maximum temperatures in the context of usual care.

Sample size: The Fever Observational Study was designed to collect data from approximately 1100 children with suspected infection. This was deemed necessary to estimate 30-day mortality with a 95% confidence interval of $\pm 1.4\%$ based on an overall crude mortality of 6% for and a primary or secondary diagnosis consistent with an infection in 51.6% of unplanned admissions (from PICANET data). This was estimated to be collected from 20 participating sites over a 6-month period. Therefore, for this thesis, the samples size was the number of children who met eligibility criteria admitted to Great Ormond Street Hospital ICUs over the 6-month period.

Data sources and collection: A case report form was designed to collect

- (a) demographic information,
- (b) eligibility criteria,
- (c) data regarding infections including culture positive results,
- (d) temperature data at admission and maximum temperature for the first 5 calendar days of admission, and
- e) anti-pyretic interventions for the first 5 days of admission

Data for (a) and (b) were collected for all children who underwent unplanned admissions. This was to characterise this population as inform the sample size calculation for the interventional trial. For those who fulfilled exclusion criteria or did not have a confirmed or suspected infection, no further data were collected. For all other children, data for (c), (d) and (e) were collected for the first 5 calendar days of admission (i.e. 00:00 to 23:59, with the day of admission as day 0; therefore, data collected for days 0-4) or until discharge from PICU if sooner.

Data regarding the mode of temperature measurement were not collected as the study was designed to be a pragmatic evaluation of temperature management across multiple sites – therefore the standard care temperature measurement was accepted.

Anti-pyretic intervention categories included paracetamol, NSAIDs, external cooling (fan, ice-packs and cooling mattress) and other (including extracorporeal circuits such as ECMO or continuous veno-venous haemofiltration: these were included even if they were not used specifically for purposes of cooling)

The paper case report form is presented as Appendix B. This was designed by the FEVER Feasibility Study team with input from the author during design.

Patients were screened daily for having unplanned admissions by the author or another member of the Critical Care Research Team. If eligibility criteria were fulfilled, daily data were filled in from the electronic health record. Culture results were added as they became available during the first 5 days of admission. The paper forms at Great Ormond Street Hospital were filled in primarily by the author with assistance from the rest of the Critical Care Research Team.

The data were manually entered and uploaded electronically as a bolt-on module to the PICANET dataset by members of the Great Ormond Street Hospital Critical Care Information Team. Outcome data were matched through PICANET by ICNARC. Data for analysis were subsequently downloaded from the PICANET portal. All data were collected for patients admitted between 1st March and 31st August 2017

Data analysis: Frequencies of patients fulfilling each stage of the eligibility criteria were described as numbers and percentages of the total number of admissions within the study period. The distribution of temperature for the first 5 days of admission were described using summary statistics (mean and standard deviation, median, inter-quartile range and range). The proportion of children with a maximum temperature $>38^{\circ}\text{C}$ was calculated. Data on anti-pyretic interventions are presented in Chapter 3. The data analysis was planned by the team

at ICNARC led by Professor David Harrison. Data for the Great Ormond Street Hospital cohort presented below was analysed by me replicating the analysis done by ICNARC for the national cohort.

Patient consent: Individual patient consent was not sought as only routinely collected data were analysed. Patients were informed of routine data collection through PICANET using leaflets and posters in the parent rooms. Patients, parents or legal representatives were able to opt out from participation and have their data removed from the study.

The Fever Observational Study was reviewed and approved by the Greater Manchester West Research Ethics Committee (ref: 17/NW/0026) and the UK Health Research Authority.

All data were analysed using Microsoft Excel (Microsoft Corp. WA, USA) and R (www.cran.r-project.org). All SQL, visual basic and R code used are detailed in Appendix A.

2.4 Results

2.4.1 Retrospective study of temperature profiles and incidence of fever:

Temperature data were collected from the electronic patient health record over a 68-month period between 1st April 2012 and 31st December 2017. Over this period the three ICU areas had 10379 admissions (5602 PICU/NICU, 4777 CICU). Of these 5602 were planned admissions and 4776 were unplanned (1 admission was not coded as either). Over half the children were <1 years of age (5689/10379, 54.8%); 1024/10379 (9.9%) were between 1-2 years; 1359/10379 (13.1%) were between 2-5 years; and 2306/10379 (22.2%) were older than 5 years. The baseline characteristics and outcomes for these children are shown in Table 2.1.

Baseline characteristics	P/NICU (n=5602)	CICU (n=4777)	Total (n=10379)
Age in months, median (IQR)	9.2 (1.2-58.7)	8.7 (2.3-45.1)	8.9 (1.6-50.9)
Age distribution, n (%)			
<1 year	2989 (53.3)	2675 (56.0)	5664 (54.6)
1-2 years	559 (10.0)	473 (9.9)	1032 (9.9)
2-5 years	672 (12.0)	678 (14.2)	1350 (13.0)
5-12 years	810 (14.5)	535 (11.2)	1345 (13.0)
>12 years	572 (10.2)	416 (8.7)	988 (9.5)
Prematurity			
<37 weeks CGA	721 (12.9)	88 (1.8)	809 (7.8)
<27 weeks CGA	50 (0.9)	0	50 (0.5)
Male, n (%)	3145 (56.1)	2599 (54.4)	5744 (55.3)
Planned admission, n (%)	2069 (36.9)	3535 (74.0)	5604 (54.0)
PIM % risk of mortality, median (IQR)	2.2 (0.8-5.3)	1.1 (0.7-2.5)	1.2 (0.7-0.42)
Categories of risk of mortality (n)			
<1%	1785 (31.9)	2071 (43.4)	3856 (37.2)
1-5%	2336 (41.7)	1991 (41.7)	4327 (41.7)
5-15%	1130 (20.2)	499 (10.4)	1629 (15.7)
>15%	351 (6.3)	216 (4.5)	567 (5.5)
Length of stay in days, median (IQR)	3 (1-7)	3 (1-7)	3 (1-7)
Mortality, n (%)	346 (6.2)	140 (2.9)	486 (4.7)

Table 2.1: Baseline characteristics of children admitted to ICU over 68-month period between April 2012 and December 2017. Age and corrected gestational age (CGA) calculated at admission.

The distribution of the number of temperature measurements in 48 hours per admission is shown in Figure 2.1. The modal number of temperatures measurements taken was 16 over the 48-hour period (i.e. on average these children had a temperature measurement every $48/16=3$ hours). Two hundred and thirty-five admissions (2.2%) did not have any recorded temperatures $\geq 32^{\circ}\text{C}$. It is possible that these children died early, or only had recorded temperatures $< 32^{\circ}\text{C}$ in the first 48 hours. Some admissions may not have recorded temperatures due to periods of the electronic health record server maintenance.

The distribution of temperature over the first 48 hours of admission is shown in Figure 2.2, with the whole range, 5th, 25th, 50th (median) 75th and 95th centiles. Temperature is relatively well controlled within the first 48 hours, with 90% of all temperature measurements between 36.4°C and 38.4°C . Temperature decreases with time post admission: there is a rise in the

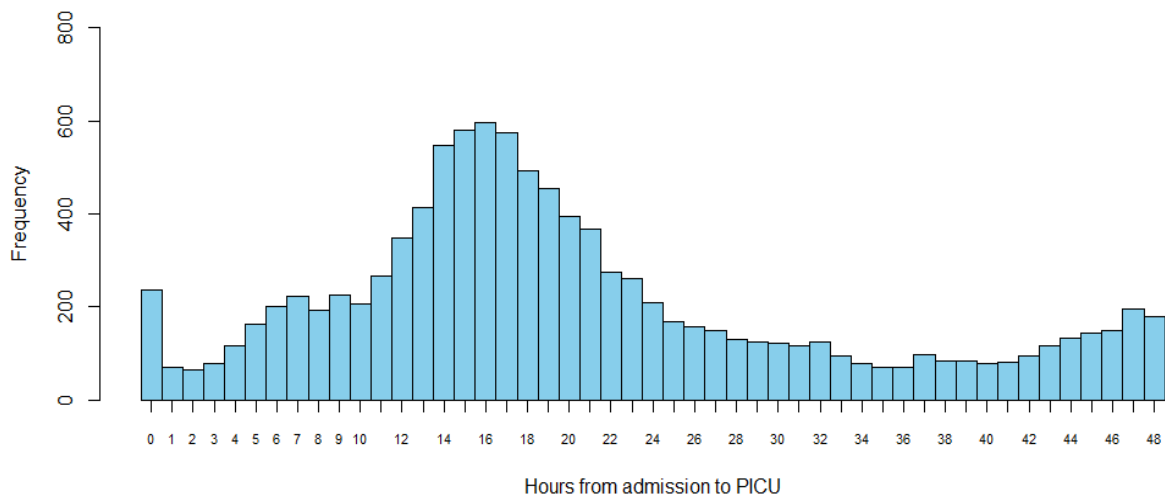


Figure 2.1: The distribution of the number of temperature measurements $\geq 32^{\circ}\text{C}$ recorded for each admission. Of the 10379 admissions, 235 had no temperature measurements $\geq 32^{\circ}\text{C}$ available. The histogram is not normalised for the number of patients at each time points i.e. some children will have been discharged or died before 48 hours: this is not accounted for.

median temperature over the first 6-8 hours post admission, followed by a decline to $< 37^{\circ}\text{C}$ after 30 hours. The peaks in profile of the upper limits of the range represent outliers (i.e. in

the top 5th centile number of measurements) given that the profile for the 95th centile values are smoother.

The distributions of temperature according to unit, type of admission and age are shown in figures 2.3, 2.4 and 2.5 respectively. Children admitted to the cardiac intensive care unit (CICU) have lower temperature at admission compared to those admitted to the general PICU/NICU. The temperature is also lower in the second 24 hours on CICU. The distributions of temperature are significantly different between units (Kolmogorov-Smirnov D-statistic 0.02, p-value < 2.2×10^{-16}). The temperatures are high early in unplanned admissions, decreasing in the second 24 hours; for planned admissions the temperatures are low at admission, rise slightly over the following 18 hours, but decrease in the second 24 hours (as with unplanned admissions). The distributions are statistically different between

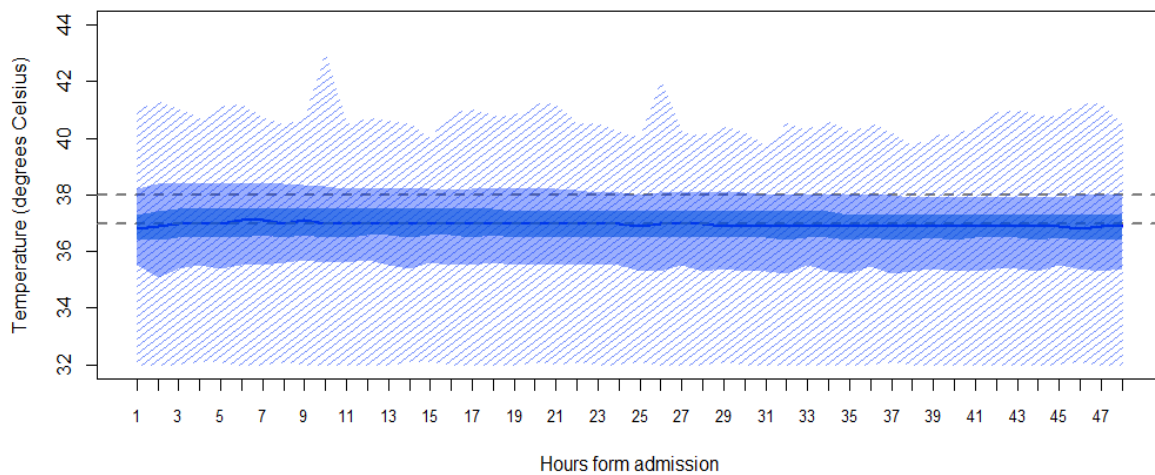


Figure 2.2: Temperature profiles over 48 hours from admission for 10379 admissions over 68 months. The blue line shows the median temperature for each hour; the darker blue shaded area represents the 25th-75th centile range; the lighter blue the 5th-95th centile range and the crosshatched area represents the range of temperatures for the whole population (measurements <32°C were excluded). The grey dashed lines are reference lines for 37°C and 38°C.

unplanned and planned admissions (Kolmogorov-Smirnov D-statistic 0.04, p-value < 2.2×10^{-16}). Infants have lower temperatures compared to children >1 year – the median temperature

for infants is mostly $<37^{\circ}\text{C}$, whereas in older children the median temperature is largely over 37°C for the first 30 hours. There is a significant difference between the temperature profiles of infants and children >1 year (Kolmogorov-Smirnov D-statistic 0.06, p-value $<2.2 \times 10^{-16}$).

Fever, defined as a temperature $\geq 38^{\circ}\text{C}$, occurred in 4066/10379 (39.2%; 95%CI 38.2-40.1%) admissions within the first 48 hours. Fever occurred early: more than half cases of fever occurred by 9 hours of admission to ICU (2177, i.e. 53.5%). The probability of fever occurring by hour is shown as time-to-event plot in Figure 2.6. The distributions of the hour when fever occurred first, and last, in the first 48 hours, are shown in Figure 2.7. While fever occurs early, fever continues to occur in a small proportion over the first 48 hours – 186/4066 (4.5%) children with fever had a temperature $\geq 38^{\circ}\text{C}$ at hour 48.

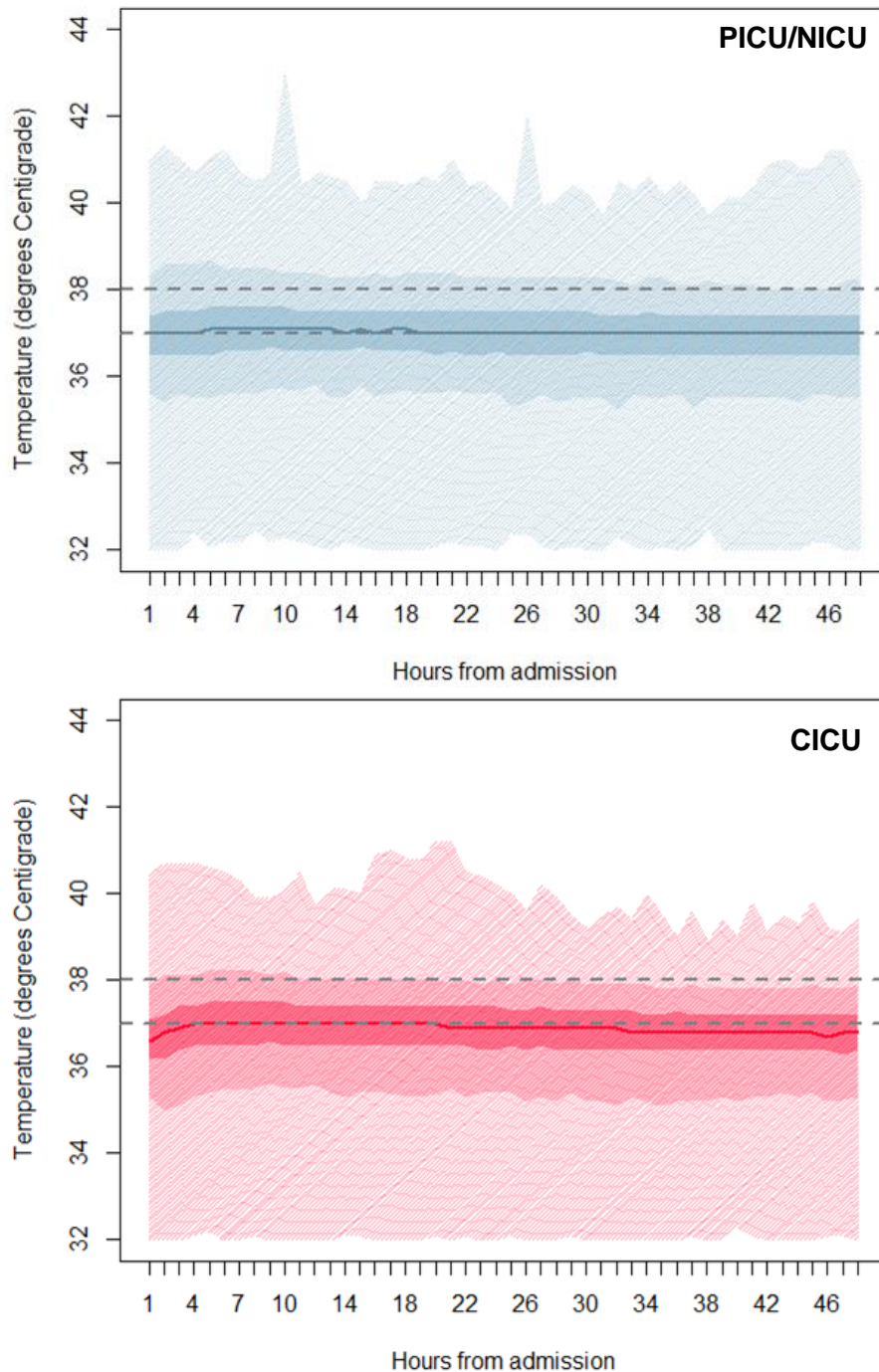


Figure 2.3: Temperature profiles over 48 hours from admission to PICU/NICU and CICU. Data shown for children admitted to PICU/NICU (top, n=5602) and CICU (bottom, n=4777) over 68 months. The solid line shows the median temperature for each hour; the shaded areas represent the 25th-75th centile range; the 5th-95th centile range and the total range of temperatures for the whole population (measurements <32°C were excluded). The grey dashed lines are reference lines for 37°C and 38°C. The distribution between the units are significantly different (Kolmogorov-Smirnov D-statistic 0.02, p-value <2.2 x 10⁻¹⁶)

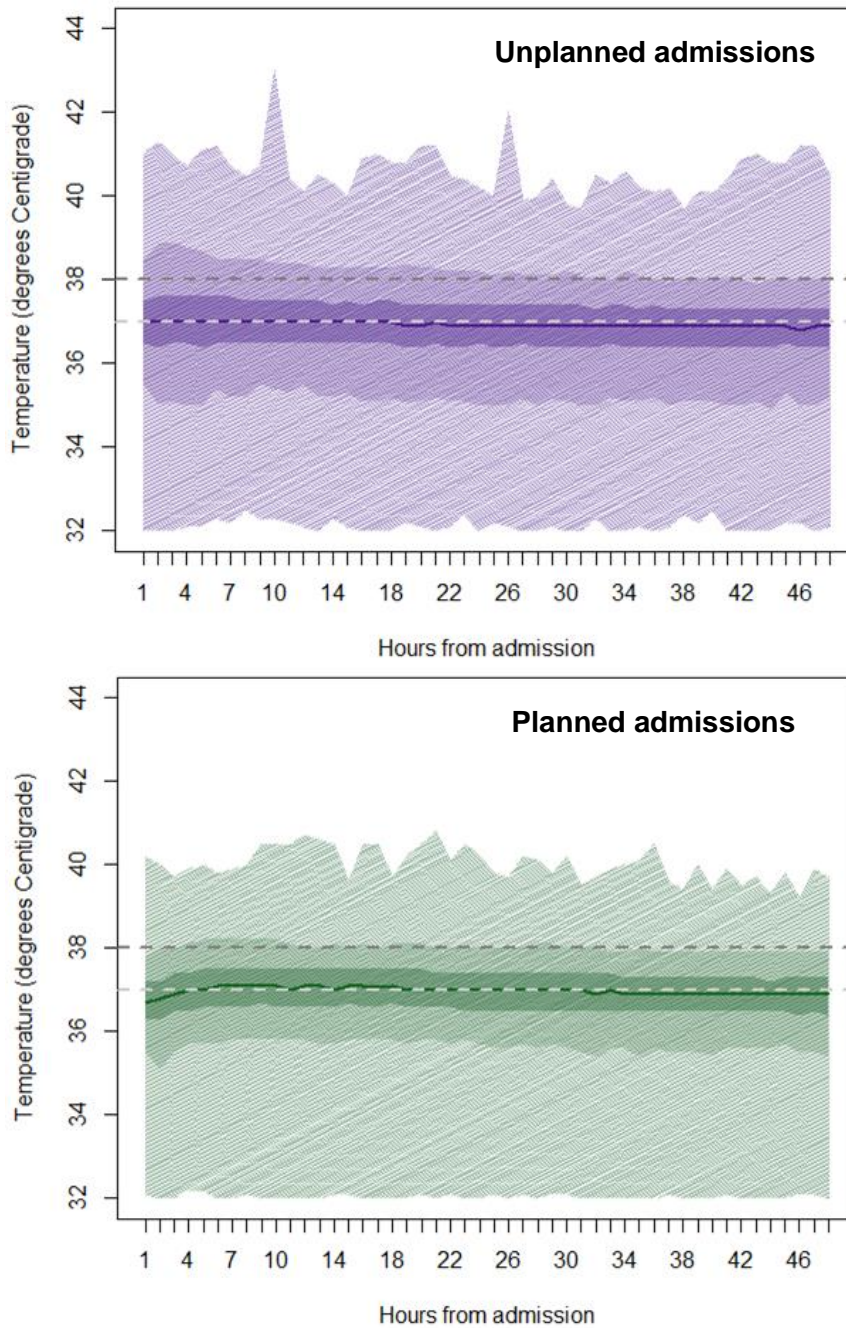


Figure 2.4: Temperature profiles over 48 hours from unplanned and planned admission to ICU. Data shown for children admitted as unplanned (top, n=4775) and planned (bottom, n=5604) admissions over 68 months. The solid line shows the median temperature for each hour; the shaded areas represent the 25th-75th centile range; the 5th-95th centile range and the total range of temperatures for the whole population (measurements <32°C were excluded). The grey dashed lines are reference lines for 37°C and 38°C. The distribution between the units are significantly different (Kolmogorov-Smirnov D-statistic 0.04, p-value <2.2 x 10⁻¹⁶)

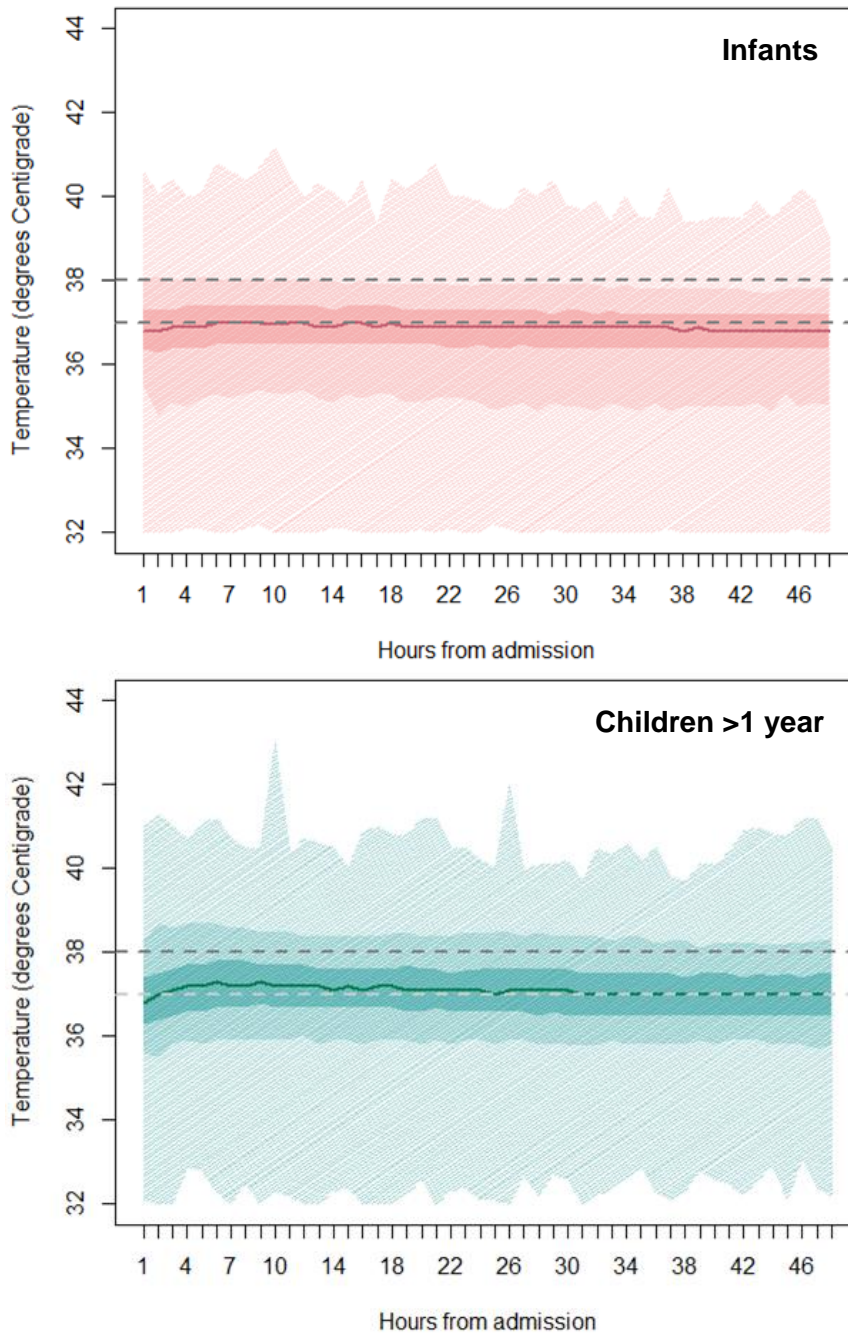


Figure 2.5: Temperature profiles over 48 hours from admission to ICU according to age. Data shown for infants (top, n=5689) and children over 1 year (bottom, n=4689) over a 68-month period. The solid line shows the median temperature for each hour; the shaded areas represent the 25th-75th centile range; the 5th-95th centile range and the total range of temperatures for the whole population (measurements <32°C were excluded). The grey dashed lines are reference lines for 37°C and 38°C. The distribution between the units are significantly different (Kolmogorov-Smirnov D-statistic 0.06, p-value <2.2 x 10⁻¹⁶)

The distribution of the number of temperature measurements $\geq 38^{\circ}\text{C}$ for each admission is shown in Figure 2.8. Most children with fever had < 3 measurements of $\geq 38^{\circ}\text{C}$ (2073/4066, 51.0%; 95%CI 49.4-52.5%). The distribution of the percentage of measurements $\geq 38^{\circ}\text{C}$ is shown in Figure 2.9, for the whole population ($n=10379$) and those with fever ($n=4066$). Even in children with fever, most children had $< 10\%$ of their temperature measurements in the febrile range.

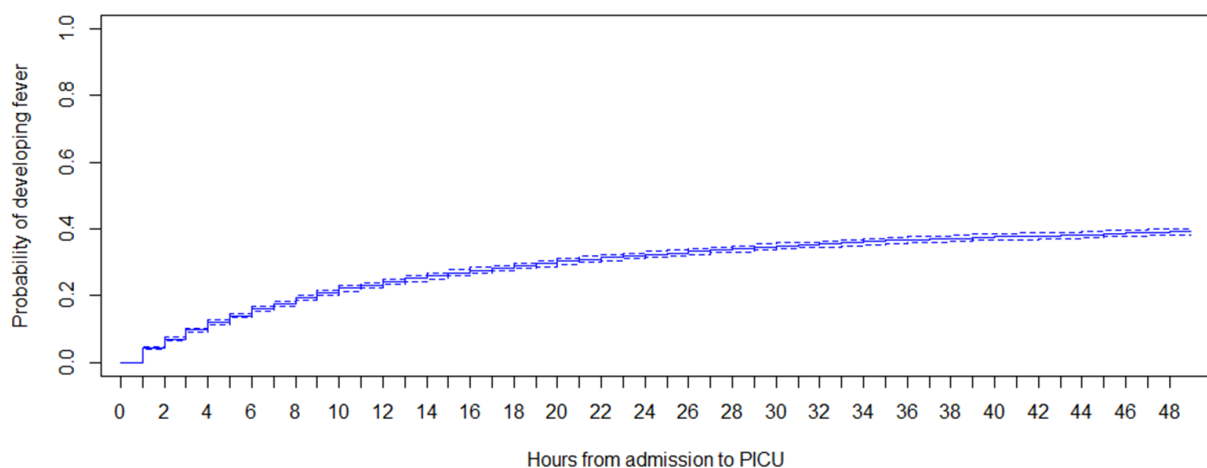


Figure 2.6: Time-to-event plot showing probability of developing a fever for the first time in the 48-hour post admission to ICU. The continuous line represents the probability of developing a fever defined as a temperature $\geq 38^{\circ}\text{C}$, while the dashed lines represent the 95% confidence intervals for the probability estimate. The overall probability of developing fever is 39.2% at 48 hours. Just over half (53.5%) the children who develop fever do so within the first 9 hours of admission.

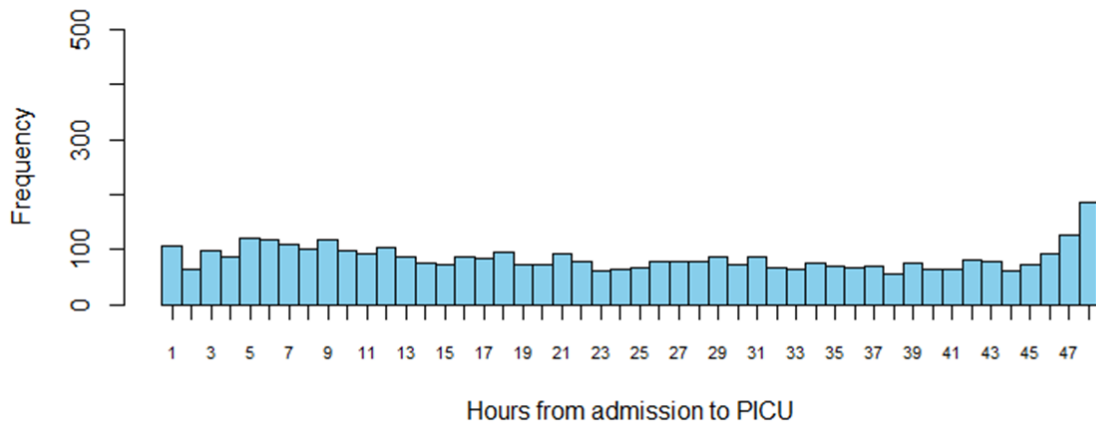
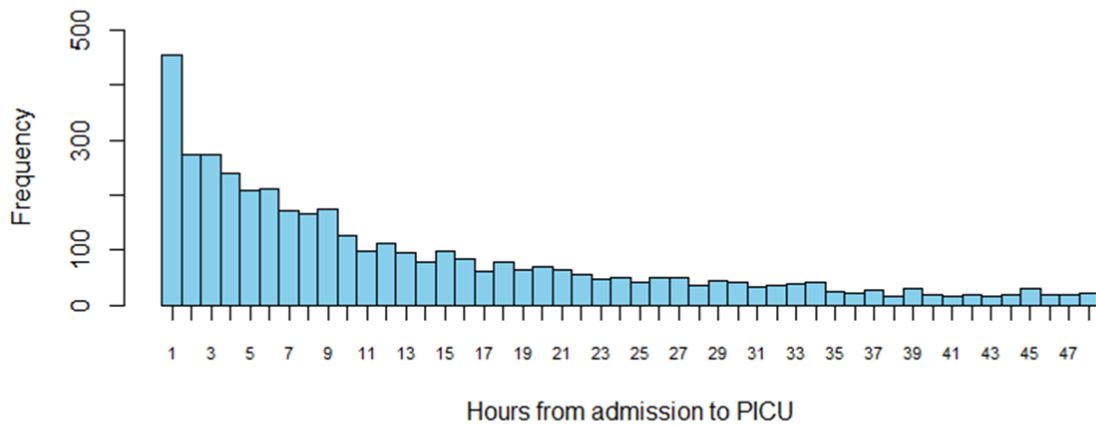


Figure 2.7: Histograms of the hour of first occurrence of fever (top panel) and final hour of fever occurrence (bottom panel) within the first 48 hours of admission to ICU. As evident from Figure 2.6, fever occurs early post admission, with over half the children with fever developing this within 9 hours of admission. However, fever continues throughout the first 48 hours, with the final measurement of temperature $\geq 38^{\circ}\text{C}$ relatively equally distributed across the 48-hour period. There were 186 children who had fever at hour 48.

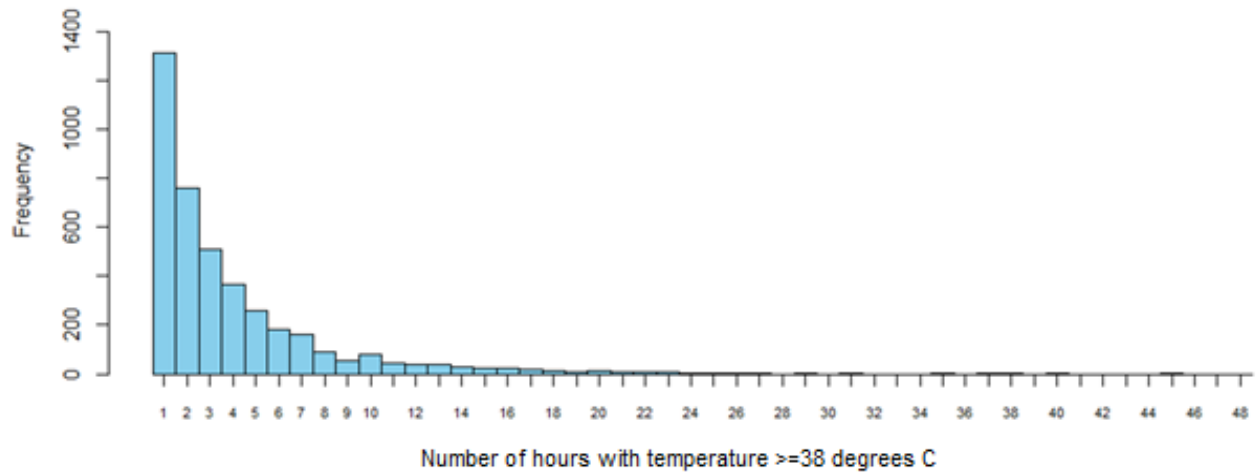


Figure 2.8: Distribution of the numbers of hours with temperature $\geq 38^{\circ}\text{C}$ in those with fever within the first 48 hours (n=4066). Most children had <3 hours of measured temperature $\geq 38^{\circ}\text{C}$ (51.0%). Twenty-one children had a 24-hours or more of a temperature $\geq 38^{\circ}\text{C}$.

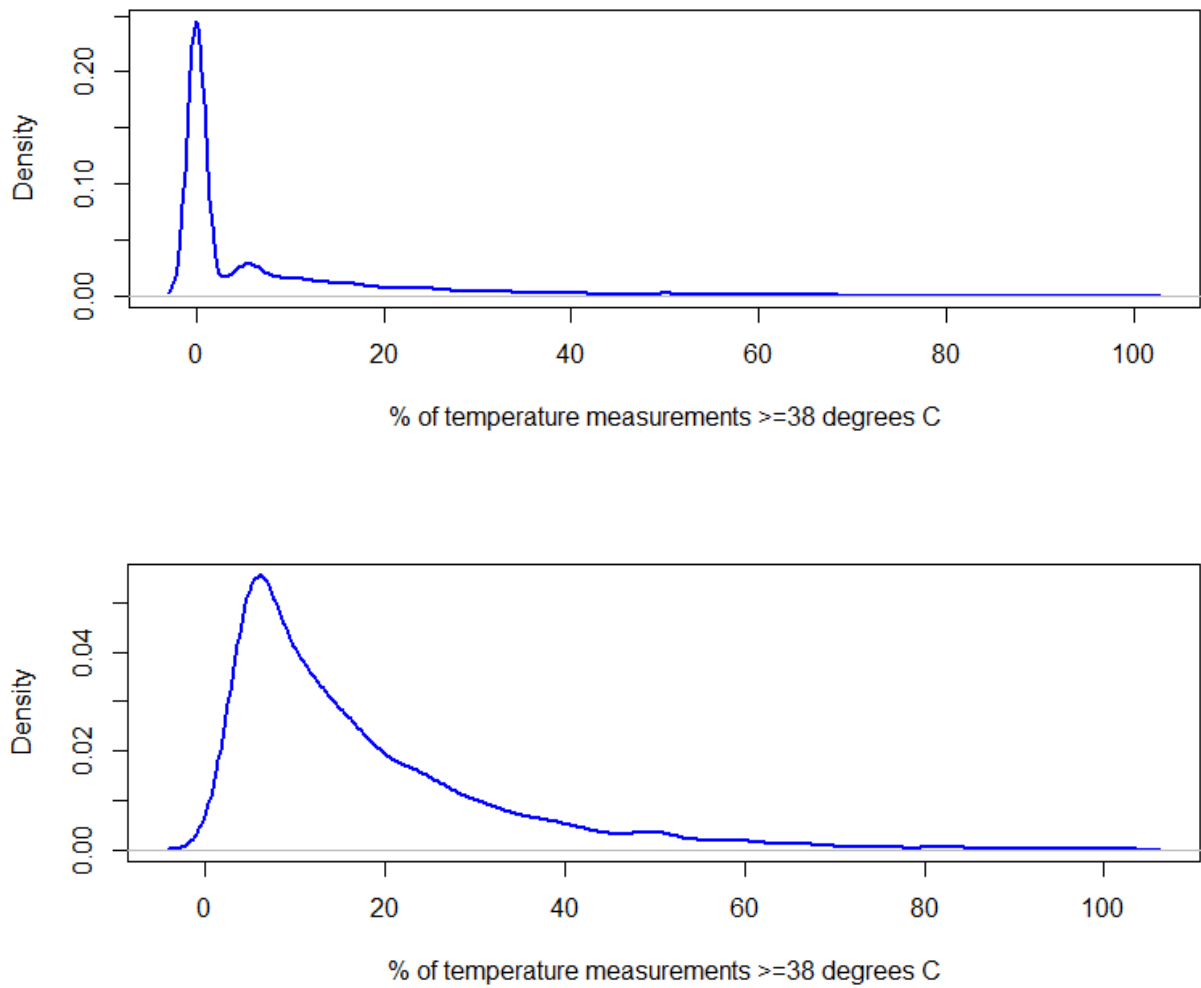


Figure 2.9: Density plot showing distribution of temperature measurements with fever (temperature $\geq 38^{\circ}\text{C}$). The top panel includes all admissions ($n=10379$), the bottom panel shows the distribution in children who have fever in the first 48 hour ($n=4066$).

2.4.2 Prospective study of temperature profile in those admitted with infection

There were 273 unplanned admissions between 1st March and 31st August 2017 at Great Ormond Street Hospital (out of a total of 876 total admissions). Of these, 78/273 (28.6%) fulfilled exclusion criteria and a further 55/195 (28.2%) did not have a suspected or confirmed infection. Therefore 140 admissions had temperature and anti-pyretic treatment data. The flow diagram for the cohort is shown in Figure 2.10.

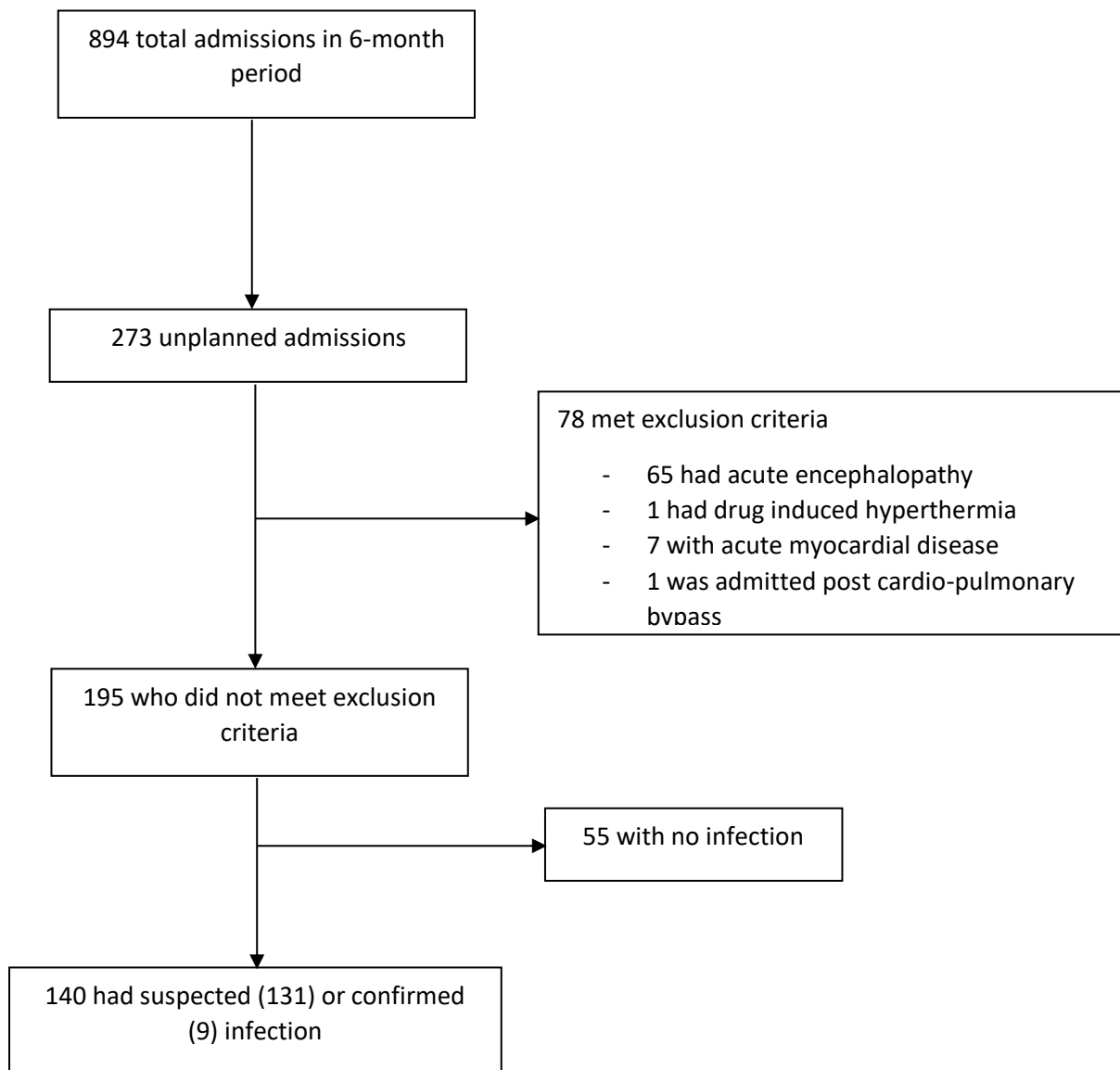


Figure 2.10: Flow diagram of children eligible for data collection in the Fever Observational Study at Great Ormond Street Hospital over the 6-month period.

The baseline characteristics of these children are shown in Table 2.2. Although the total cohort was slightly older than the retrospective study cohort presented in the previous section, the eligible children were younger. The length of stay and mortality was higher in this study compared to the retrospective study cohort, which may be explained by the fact that only unplanned admissions were part of the Fever Observational Study.

Baseline characteristics	Total GOSH cohort (n=273)	Eligible children (n=140)
Age in months, median (IQR)	12.4 (1.0-61.3)	3.8 (0.4-23.8)
Age distribution, n (%)		
<1 year	135 (49.5)	87 (62.1)
1-2 years	34 (12.5)	18 (12.9)
2-5 years	33 (12.1)	9 (6.4)
5-12 years	47 (17.2)	16 (11.4)
>12 years	24 (8.8)	10 (7.1)
Prematurity, n (%)		
<37 weeks CGA	26 (9.5)	21 (15)
<27 weeks CGA	5 (1.8)	5 (3.5)
Length of stay in days, median (IQR)	4 (3-9)	5 (3-11)
Mortality, n (%)	38 (13.9)	22 (15.7)

Table 2.2: Baseline characteristics of children with unplanned admissions and met eligibility criteria for the Fever Observational Study at Great Ormond Street Hospital. Age and corrected gestational age (CGA) were calculated at admission. Sex and PIM risk of mortality data were not available.

The summary statistics of the admission and maximum temperatures each day are shown in Table 2.3 and the distribution of maximum temperatures are shown in Figure 2.11. The

range of temperature narrowed over time, suggesting a reduction in temperature variability on PICU. In total 77/140 (55.0%; 95%CI 46.8-63.2%) children had a fever. The distribution of children who had a fever (i.e. maximum temperature $\geq 38^{\circ}\text{C}$) on each of the days is shown in Figure 2.12. The largest proportion of children were febrile on day 1 (45/133, 33.8%), with the incidence of fever dropping thereafter (29.4% on day 0, 21.2% on day 2, 21.5% on day 3 and 16.9% on day 4) (Table 2.4).

The number of children who developed a new fever declined over time: 40 on day 0, 17 on day 1, 8 on day 2, 6 on day 3 and 3 on day 4.

	Admission temp ($^{\circ}\text{C}$)	Maximum day 0 temp ($^{\circ}\text{C}$)	Maximum day 1 temp ($^{\circ}\text{C}$)	Maximum day 2 temp ($^{\circ}\text{C}$)	Maximum day 3 temp ($^{\circ}\text{C}$)	Maximum day 4 temp ($^{\circ}\text{C}$)
n	140	140	134	118	94	77
Mean	36.76	37.67	37.91	37.68	37.60	37.65
Standard deviation	1.25	0.81	0.71	0.59	0.53	0.46
Median	36.90	37.50	37.80	37.60	37.60	37.70
Inter-quartile range	34.40- 37.45	37.20- 38.00	37.40- 38.30	37.40- 37.90	37.30- 37.90	37.30- 37.90
Range	29.40- 40.40	35.90- 40.50	36.40- 40.30	36.40- 39.90	36.20- 39.20	36.50- 39.00

Table 2.3: Summary statistics of temperature eligible children in the Fever Observational Study cohort at Great Ormond Street Hospital. Although the mean and median peaked on day 1, they remained stable between $37.5\text{-}38.0^{\circ}\text{C}$. The range and inter-quartile range became narrower over time, suggesting a reduction in temperature variability on PICU.

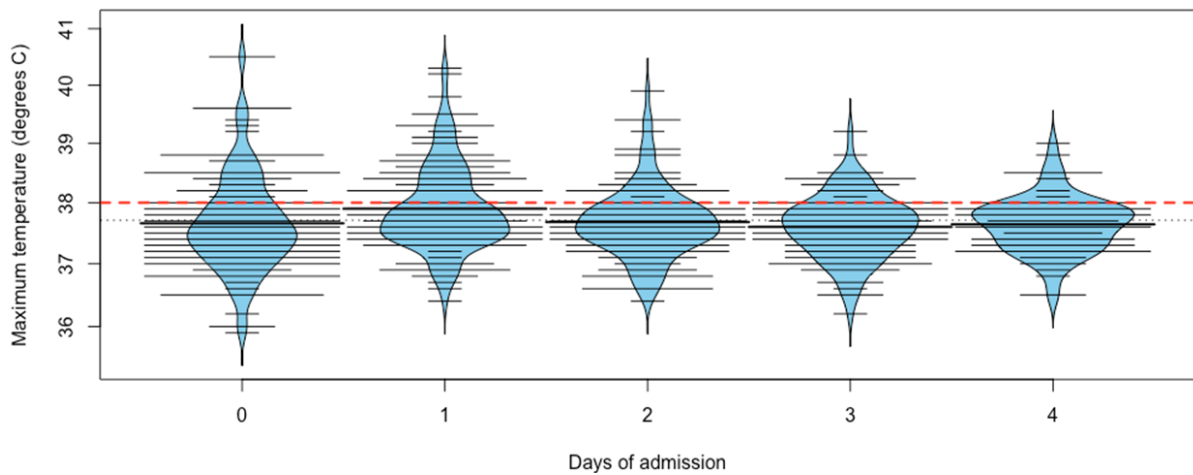


Figure 2.11: Beanplots showing the distribution of maximum temperatures over the first 5 days of PICU stay. Children were included if they had unplanned admissions with suspected or confirmed infection and without exclusion criteria (encephalopathy, myocardial disease, rhabdomyolysis or perceived imminent death) $n=140$. The black dotted line shows the median value, the red dashed line represents 38°C . The thick line for each beanplot represents the median value for each day: the median value is close to 38°C on day 1 but decreases thereafter.

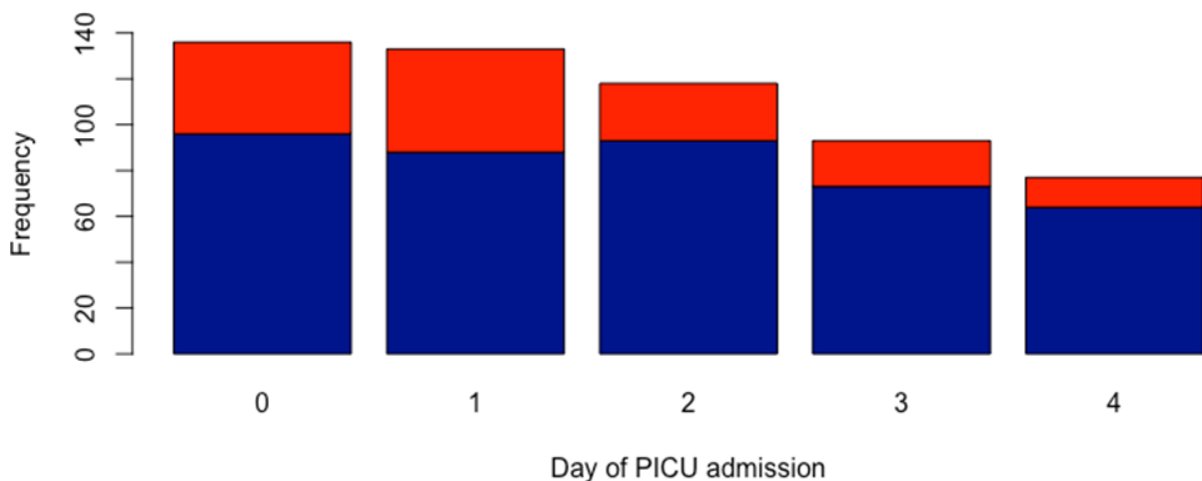


Figure 2.12: Frequency of children with fever and no fever according to day of PICU admission in the cohort of the Fever Observational Study. The blue lower segments represent the number of children with a maximum temperature $<38^{\circ}\text{C}$; the red upper segments represent the numbers of children with a maximum temperature $\geq 38^{\circ}\text{C}$.

	Day 0	Day 1	Day 2	Day 3	Day 4
Number of children with temperature data	136	134	118	94	77
Number of children with fever (%)	40 (29.4)	45 (33.6)	25 (21.2)	20 (21.3)	13 (16.9)
Number of children with new fever (% of children with fever)	40	17 (37.8)	8 (32.0)	6 (30.0)	3 (23.1)

Table 2.4: Number of children with fever on each day of admission. The table shows the number of children with fever each day, including those with a new fever (i.e. no temperature $>38^{\circ}\text{C}$ on previous days of admission). Day 0 is the first calendar day of admission. Four children had temperature data missing on day of admission.

2.5 Discussion

2.5.1 Summary of results

Incidence of fever in children on ICU: In an unselected population, just under 40% of children had a fever (temperature $\geq 38^{\circ}\text{C}$) within the first 48 hours of admission to the intensive care unit. Over half the episodes of fever occurred within the first 9 hours of admission, with the rate of new fever declining thereafter. Most children had <3 temperature measurements $\geq 38^{\circ}\text{C}$ i.e. this was less than 10% of all temperature measurements. Therefore, although fever is common, it is well controlled in the ICU. Temperatures are higher in children on P/NICU, those following unplanned admissions and in children >1 year of age.

In a more selected population with confirmed or suspected infection, 55% of the children had a fever. The likelihood of fever diminished over the first 5 days, including the likelihood of a new fever. The median temperature in this population remained similar over 5 days, but the variability decreased.

2.5.2 Hypothesis testing and Implications of results in critically ill children

The aim of these analyses was to understand the epidemiology of fever in children admitted to ICU. In doing so the following hypothesis was tested:

The prevalence of fever in PICU is at least comparable to the only reported paediatric incidence of 40%, with fever occurring early during ICU admission: The null hypothesis can be accepted. The prevalence of 39.2% in our cohort is strikingly similar to the figure quoted by Laupland et al in their similar large dataset study (44%), and the only other paediatric study (40%). Circiumaru et al's prospective study in adult ICU and Diringer et al's study in their neurosurgical ICU found a prevalence of 70% - however their cohort size was small in the former, with a highly specialised population in both.

In a more selected population with suspected infection, the prevalence of fever was higher, at 55%. This was part of the Fever Observational Study, conducted over 22 sites in total – data from Great Ormond Street Hospital were shown in the results above as these data were primarily collected by the author. The overall prevalence of fever across all 22 sites was 873/1841 (47.4%). Therefore, in our unit the prevalence in this population is higher than the collective average. In addition to fever being more common in children with infection, the decline in fever is slow – even on day 4, 16.9% had a fever and 23% of the children developed a new fever. In contrast, by 48 hours, 95% of the unselected population had a temperature $<38^{\circ}\text{C}$. This is in keeping with Gordijn et al's description, where 92.7% of children developed fever within the first 48 hours of admission; the remaining children developed a new fever 7 days post admission on average, suggesting a nosocomial infection [Gordijn 2008].

Even within the first 48 hours, fever occurs early. Over half the children who develop fever in the first 24 hours do so within the first 9 hours as seen in the time-to-event curve in Figure 2.7 and the histogram in Figure 2.8. When it does occur, fever is short-lived in ICU. Most children have only a single measurement of a temperature $\geq 38^{\circ}\text{C}$ (Figure 2.9). Overall, only 10% of temperature measurements $\geq 38^{\circ}\text{C}$ in the first 48 hours as seen in the density plots in Figure 2.10. This may be due to temperature management in the ICU. Alternatively, it may

reflect the natural history of fever: either recovery from critical illness, or a switch to conserve energy during critical illness.

There is a difference between the temperature profiles between children admitted to general and cardiac ICU. Children in general ICU are hotter, with the 95th centile >38°C for majority of the 48-hour period. In contrast, children on cardiac ICU start cold, with temperature increasing over the first 4 hours until the first 12 hours, after which the variability in temperature decreases. This is likely to represent children being admitted post cardio-pulmonary bypass, with relatively low temperatures. The rise in temperature coincides with the described nadir in cardiac output in children post cardio-pulmonary bypass [Wernovsky 1995], which in turn corresponds with the levels of pro-inflammatory cytokines such as interleukin-6 and interleukin-8 [Hovels-Gurich 2002]. A similar pattern is seen between unplanned and planned admissions: this reflects that the majority of unplanned admissions occur in general ICU, whereas cardiac ICU admissions are largely planned. Infants have lower temperatures compared to children over 1 year of age, with a median temperature consistently <37°C in infants. This is consistent with greater heat loss in smaller children due to a greater surface area to weight ratio. It is also possible that infants do not have sufficient capacity for heat production, especially when critically unwell. The infant population also include premature children from the neonatal ICU at Great Ormond Street Hospital, in whom thermoregulatory mechanisms may be particularly poor.

2.5.3 Limitations

There are several limitations with each of the methodologies used:

- 1) The true prevalence of fever in ICU cannot be ascertained without considering the use of anti-pyretic interventions. To reveal the true prevalence of fever in critical illness, all anti-pyretic interventions would need to be limited. Nevertheless, the data

presents a pragmatic account of fever on the ICU, with current practices of fever management and paracetamol use.

- 2) In none of the studies was the mode and site of temperature measurement accounted for. While peripheral and skin temperatures were excluded, core (rectal, oesophageal and bladder) temperatures were treated as equivalent to axillary and tympanic temperatures. Previous data have demonstrated a difference between core and axillary and tympanic temperatures; however, this bias had 95% limits of agreement that crossed 0. This was accepted, especially given that almost 80% of temperature measurements were axillary. It is nevertheless possible that the differences in temperature described, either in the 48 hours profile or the maximum daily temperatures in the prospective study may be confounded by different modes of temperature measurement. It is unlikely to switch back and forth between continuous core monitoring and axillary temperatures: in many cases continuous core temperature monitoring is intermittently verified using axillary temperatures. Core monitoring is more likely in the early part of the admission when the child is most unstable - therefore, the temporal changes over the first 48 hours could be affected by the site of measurement if the oesophageal probe is removed within the first 24 hours.
- 3) Fever is defined as a temperature $\geq 38^{\circ}\text{C}$. Whilst a temperature-based definition of fever is universally used, fever is a change in the temperature set-point. Therefore, a relative temperature difference may be a more accurate definition of fever – e.g. in a child who has a temperature of 35°C at baseline, a temperature of 37°C may represent a fever. No measurements of inflammatory cytokines were taken to demonstrate an inflammatory process.
- 4) Fever occurs early after admission. Doses of paracetamol given just prior to admission were not accounted for. The greater incidence of fever early in admission may reflect the wearing-off of the effect of paracetamol given prior to admission.

5) Methodological considerations: Retrospective data were collected from the Electronic Health Record. While this allows data to be collected for a large number of children, it does restrict the amount and type of data collected, for example infection status, which is not recorded systematically. For this reason, data were collected prospectively in the Fever Observational Study. Prospective data collection allows detailed data collection in a better-defined study cohort. In this case, eligibility was restricted to a potential trial population to test fever management. However, prospective data collection does restrict the length of time over which detailed data are collected. No comparison was planned a priori between the cohorts as the prospective cohort was likely to represent a sub-sample of the population sampled retrospectively. Post-hoc comparison of the maximum temperatures in the first 2 days of admission (first 48 hours of admission for retrospective data, and days 0, 1 and 2 for prospective data) is shown in Figure 2.20. As evident from the distributions, very few children have a maximum temperature $<36.5^{\circ}\text{C}$ in the prospective cohort. This may demonstrate a genuine difference between the unselected retrospective cohort and the more defined prospective cohort – those with low temperatures may have been children expected to die soon after admission or those post-cardiopulmonary bypass surgery. The low temperatures are present even when considering unplanned admissions only. When compared statistically using a Kruskal-Wallis test, there is no difference between the unselected retrospective cohort, the unplanned sub-group and the prospective cohort ($p=0.57$). However, the prospective cohort is significantly different when compared with the unselected retrospective cohort using a Mann-Whitney test ($p=5 \times 10^{-7}$) and the unplanned admission sub-group (1×10^{-4}). The lower temperatures in the retrospective cohort may be due errors in charting which could not be verified, mislabelled temperatures (peripheral or skin temperatures labelled as axillary) or admission mis-labelled as unplanned. Retrospective data were collected using an SQL query and data were

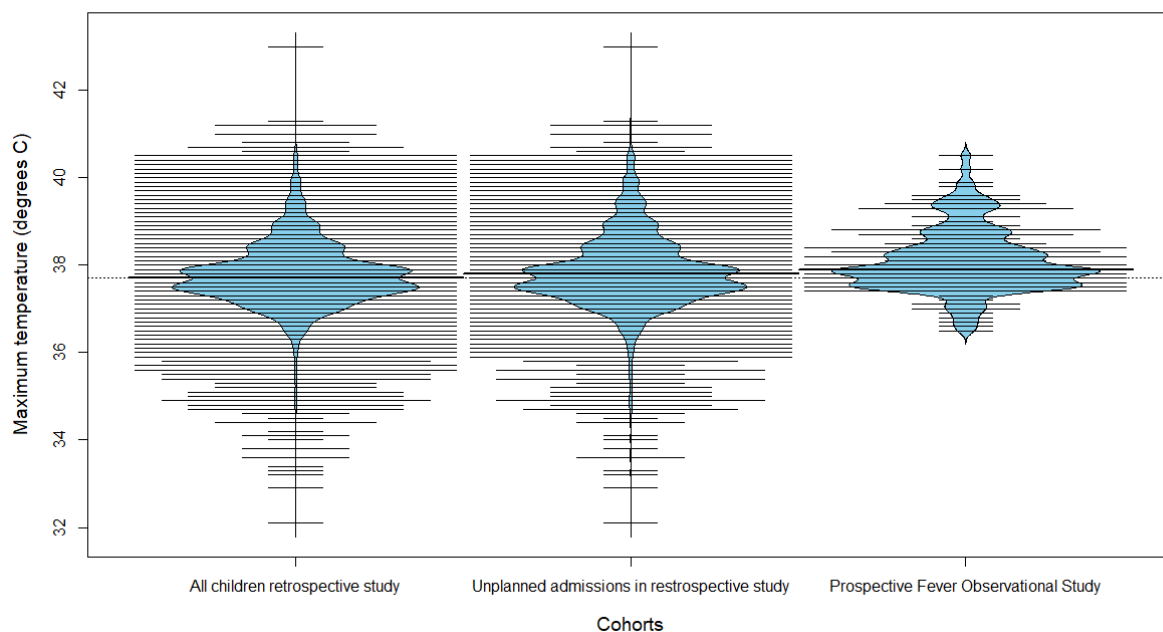


Figure 2.13: Comparison of the distribution of maximum temperatures in the first 48 hours in the different study cohorts. Beanplot showing the distribution of maximum temperature in a) all children in the retrospective cohort, b) only those with unplanned admissions in the retrospective cohort, and c) children in the prospective Fever Observational Study Great Ormond Street Hospital cohort, limited to days 0, 1 and 2. There is no difference between all 3 cohorts using a Kruskal Wallis test (p -value = 0.57), but the prospective cohort is significantly different from retrospective cohorts (Mann-Whitney p -value = 5×10^{-7} when compared against all retrospective children; p -value = 1×10^{-4} compared against unplanned admissions only)

sorted and processed using Visual Basic in Excel. The data were manually verified in a small number of cases (<5%) to determine accuracy but it is possible that data may be corrupted in processing.

- 6) Sub-group analyses: The sub-group analyses of 48-hour temperature distributions were carried out between three sub-groups that were expected to have roughly equal proportions. The paediatric and neonatal units were considered together as this is

how data are submitted to PICANET and for a large part of the time period both units were managed by the same medical team. Neonates, especially premature neonates may have immature thermoregulatory mechanisms and are nursed in temperature-controlled incubators. This may influence the results. However, less than 1% of the population were extremely premature, the group of children who are likely to have the least thermoregulatory control. Children on cardiac ICU were likely to have different temperature profiles as most children are admitted post cardiopulmonary bypass and therefore have a defined insult and may be re-warming post induced hypothermia. Unplanned admissions serve as a surrogate to those with a high likelihood of infection. Kolmogorov-Smirnov tests were used to compare distributions. While this test is used for this purpose, particularly to determine differences from characteristic distributions such as the normal distribution, it may be too sensitive in detecting clinically relevant differences. All three sub-group comparisons yielded statistically significant results. However, the interquartile range for each sub-group were clinically similar, with temperatures being maintained in narrow range. The test of statistical significance could be over interpreted beyond relatively subtle differences in the timing and proportions of febrile children.

2.6. Conclusions

The objective of this chapter was to describe the epidemiology of fever in children admitted to ICU. The study was done in a single centre. Fever occurs in 40% of all children and 55% of those admitted with infection. It occurs early, with the incidence diminishing with time.

From the epidemiological data presented in this chapter, it is evident that any changes in oxygen delivery or consumption with fever will affect a large proportion (>40%) of the PICU population. These changes will occur early but do not persist for long into the ICU admission. The data are taken in the context of standard care: fever may have been treated or even prevented using anti-pyretic drugs or cooling interventions. In the next chapter I will therefore

explore the epidemiology of the treatment of fever and evaluate the effect of anti-pyretic interventions.

Chapter 3: The epidemiology and effect of the treatment of fever in the paediatric intensive care unit

3.1 Introduction

In the previous chapter I demonstrated that fever occurs in just under 40% of children admitted to PICU and 55% in a more defined cohort of children following an unplanned admission with infection. However, this needs to be interpreted in the context of anti-pyretic treatment. Fever may be suppressed or prevented, either with the motivation to reduce a perceived imbalance between oxygen consumption and delivery, or to maintain 'normal' vital signs. In addition, some interventions may control temperature as a secondary effect rather than be used for this primary purpose: for example, continuous renal replacement therapy and extra corporeal membrane oxygenation both control temperature although rarely used for this purpose. Paracetamol and ibuprofen may be used for analgesia, with temperature control being a secondary effect. The magnitude of this temperature effect is not known, particularly in PICU. If the motivation to treat fever in critical illness is to reduce energy consumption and/or to improve haemodynamic states, then it is important to know whether the treatment is effective.

In this chapter, I will describe the epidemiology of the treatment of fever in children admitted to PICU at Great Ormond Street Hospital, London. I will do this using data from prospectively collected data from the Fever Observational Study described in the previous chapter. In addition, I will describe the frequency of use of paracetamol in the intensive care unit and evaluate its anti-pyretic effect.

3.2 Aims and hypothesis

Aims of the study:

- (i) To describe the use of anti-pyretic treatment on PICU
- (ii) To describe the use and effect of paracetamol on temperature in PICU

Null hypotheses:

Paracetamol is the most commonly used anti-pyretic treatment in PICU

Paracetamol is associated with a temperature reduction by $\geq 0.5^{\circ}\text{C}$ and compares favourably to use of no paracetamol in reducing temperature

Alternative hypotheses:

Paracetamol is not the most commonly used anti-pyretic treatment on PICU

Paracetamol is not associated with a temperature reduction by $\geq 0.5^{\circ}\text{C}$ and temperature does not reduce more than when paracetamol is not used

3.3 Methods

3.3.1 Prospective study of antipyretic use in those admitted to PICU with infection

This was part of the Fever Observational Study as described in Chapter 2. Only data collected from Great Ormond Street Hospital were used. The design, setting and population are the same as described previously in section 2.3.2.

Data sources and collection: Data were collected using the case Report Form as described in Chapter 2 and shown in Appendix B. This included anti-pyretic interventions for the first 5 days of admission. Anti-pyretic intervention categories included paracetamol, NSAIDs, external cooling (fan, ice-packs and cooling mattress) and other (including extracorporeal circuits such as ECMO or continuous veno-venous haemofiltration: these were included

even if they were not used specifically for purposes of cooling). While one of the aims of the study was to define the temperature threshold at which fever was treated, pragmatically this was likely to be difficult as it may vary between clinical shifts in the same child and therefore difficult to capture for each episode of fever. Instead, this was planned to be inferred from the maximum temperature for each day and the use of anti-pyretic interventions each day.

Bias: Information bias is introduced as it is not known whether the decision to use anti-pyretic interventions was in response to the temperature or they were used for a primary purpose other than temperature management: i.e. whether paracetamol was used regularly for analgesia or whether the child was on extra-corporeal life support. Inferences were made statistically to try and determine whether the use of anti-pyretic interventions were influenced by temperature (see below).

Data analysis: The aim of the study was to describe the use of anti-pyretic interventions and define the temperature threshold at which they were used. Anti-pyretic use was described as the proportion of patients receiving any anti-pyretic intervention, above and below a continuous range of daily maximum temperatures between 36.0-39.5°C.

The case report form did not collect information on the indication for each intervention. Therefore, it is possible that interventions were used for purposes other than temperature reduction. For example, paracetamol could have been used as an analgesic – it would be inaccurate to infer that the maximum temperature therefore fully informed the decision to use it. To explore whether the maximum temperature was associated with the use of anti-pyretic interventions, comparisons were made between the maximum daily temperatures when anti-pyretic interventions were used but not used on the previous day. If the maximum temperature was higher on the day of anti-pyretic use compared the day before when it was not, it would suggest that temperature did inform the use of anti-pyretics. This could not be done in children who received anti-pyretics on day 0 – these children were excluded as part of this analysis. For the remaining children, the maximum temperature on the day that they

first received an anti-pyretic intervention, and on the preceding day was presented as a cumulative distribution function.

3.3.2 Retrospective observational study of paracetamol use and the effect on temperature

Design: This was a retrospective observational study of the use of paracetamol in an unselected PICU population at Great Ormond Street Hospital over a 40-month period.

Setting: The study was taken across all three ICU areas i.e. the general paediatric (PICU), neonatal (NICU) and cardiac (CICU). There was no written protocol for fever management or temperature control, although the use of anti-pyretic interventions was described in the previous prospective observational study.

Patient population: Data from all children who received paracetamol and were admitted to the PICU/NICU and CICU at Great Ormond Street Hospital between 1st September 2012 and 31st December 2015 (40 months) were included. This interval was used as the Electronic Health Record at Great Ormond Street Hospital started recording drug delivery data from 1st September 2012 and the study was undertaken in 2016.

Data collection: Data were collected from electronic health records. Data were searched for the recorded administration of paracetamol using SQL (Appendix A). All paracetamol doses were included, regardless of route of administration (enteral or intravenous). Paracetamol dose data as well as the weight of patient, Paediatric Index of Mortality (PIM) score and unit (cardiac or general paediatric/neonatal ICU) were collected. Temperature data were collected for the same period to analyse the decrease in temperature following paracetamol, and in cases of fever where paracetamol was not given. As previously, temperatures labelled peripheral or skin, or unlabelled, were excluded. Temperatures recorded below 32°C were excluded, as these were likely to be either due to external cooling, or mis-labelled peripheral or skin temperatures.

Bias: Data were collected from the electronic health record to reduce recall bias. However, given the retrospective nature of the study, the exact timing of the drug administration may lack accuracy, as the recording time may vary from the administration time. The systematic bias would be towards paracetamol being recorded as being given after it was administered (rather than before). This was minimised by collecting temperature data up to 4-hours after the administration time. If paracetamol doses were given within a 6-hour period of the previous dose, there may have been a temperature effect from both doses: this was not accounted for. Data regarding other temperature control measures, such as environmental measures or surface cooling were not collected, as the aim was to quantify the effect of paracetamol in the 'real-world' setting i.e. the effect of paracetamol within the context of other temperature control mechanisms.

Sample size: A sample size calculation was not made as all data available from the electronic health record available at the time of analysis was being used.

Data analysis: Data were organised as following using Visual Basic in MS Excel:

- (i) For all doses of paracetamol, hourly temperature for 6 hours in relation to each paracetamol dose (Group P): i.e. each hour for the hour before the dose was given (time-point -1), the hour of the dose (time-point 0), and 4 hours following the dose (time-points 1-4).
- (ii) As not all paracetamol doses were given for fever, the sub-group of patients who received paracetamol and had a temperature $>38^{\circ}\text{C}$ at time-points -1 or 0 were analysed separately (Group P|F, paracetamol given with fever).
- (iii) In addition, incidences of fever (temperature $\geq 38^{\circ}\text{C}$) were identified where paracetamol was **not** given 6 hours before or after the recorded temperature (Group F). Temperature data an hour before, and 4 hours after such instances were collected.

Mann-Whitney U tests were used to compare weight and PIM score for children in Groups P|F and F to identify indication bias for paracetamol use in fever. A chi-squared test was used to compare the units, i.e. cardiac versus general paediatric and neonatal ICU, where the doses were given.

Temperature data were analysed using multi-level linear regression, with temperature as the dependent variable, time in relation to paracetamol (in Groups P and P|F) or fever (in Group F), weight and PIM score as the fixed effect variables and dose identifier and unique patient identifier as the random effect variable (Figure 3.1). This allowed for the evaluation of the mean change in temperature for each hour from time-point 0 for four hours, despite missing temperature values, while accounting for weight, and PIM as a marker of severity of illness. Inclusion of the individual patient identifier accounted for individual patient effects.

Subgroup analyses for intravenous and enteral doses of paracetamol were separately undertaken. The effect of the dose of paracetamol was analysed separately, using the dose per kilogram of paracetamol given in an interaction term with time as the fixed effect variable, in children who received paracetamol. Models with and without the interaction term were compared using the likelihood-ratio test statistic.

The separate models do not assess any affect of paracetamol on temperature reduction compared to when there was no paracetamol used. To do this the temperature changes following fever with or

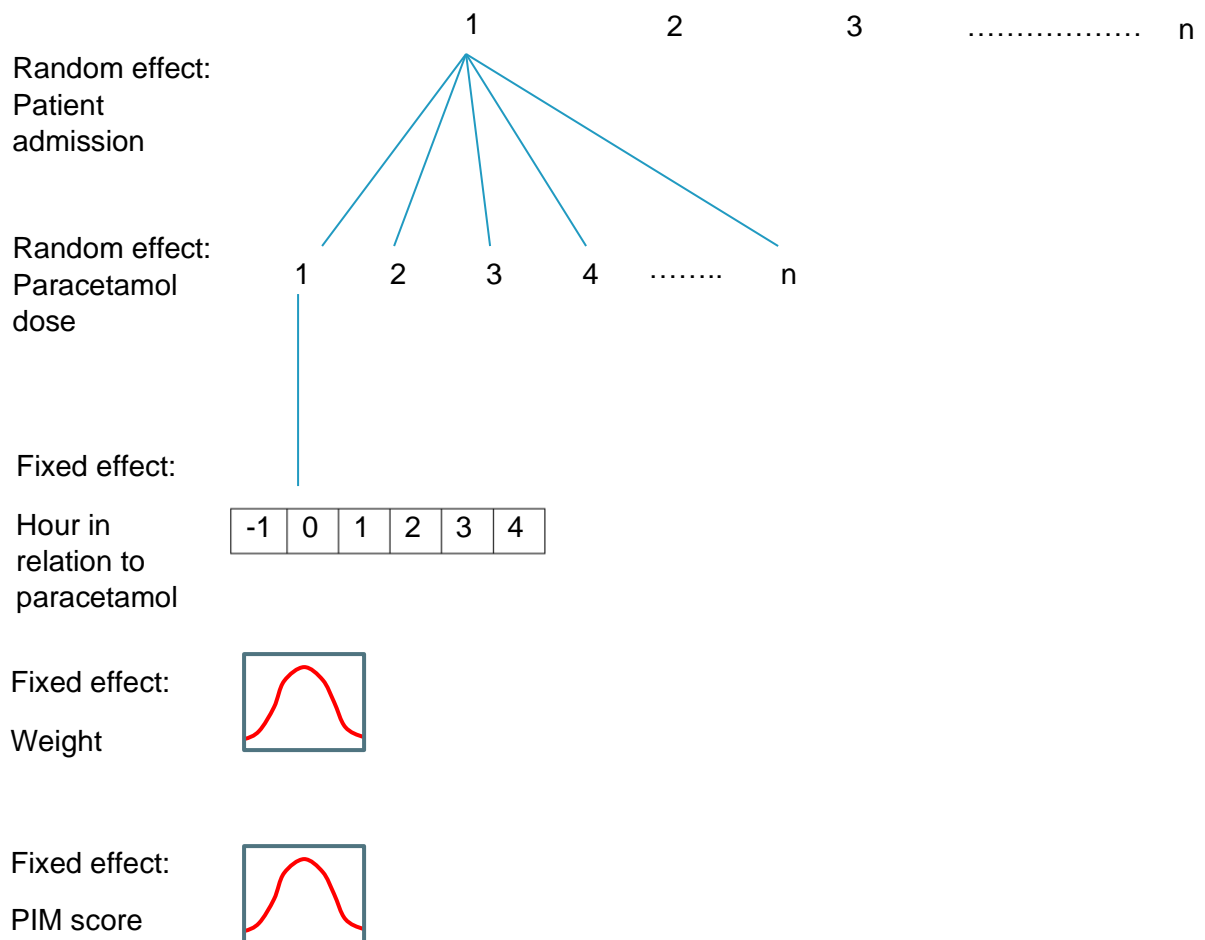


Figure 3.1: Schematic of multi-level model exploring effect of paracetamol on temperature in children admitted to ICU. Temperature was the dependent variable, hour in relation to paracetamol, weight and PIM were used as fixed effect variables; dose identifier and patient admission identifiers were used as random effects variables.

without paracetamol was compared using the likelihood-ratio test statistic. Comparisons were made between the following models (a) a multi-level regression model for all children with fever, i.e. groups P|F and F combined, with temperature as the dependent variable, time in relation to paracetamol (in Group P|F) or fever (in Group F), weight and PIM score as the fixed effect variables and dose and unique patient identifier as the random effect variable; and (b) the same model, including an interaction term for paracetamol use and time as a

fixed effect variable. Accepting the null hypothesis, i.e. a likelihood ratio test statistic close to 0, would suggest that paracetamol has a non-significant effect on change in temperature in children with fever.

All data were analysed using Microsoft Excel (Microsoft Corp. WA, USA) and R (www.cran.r-project.org). All SQL, visual basic and R code used are detailed in Appendix A.

Patient consent: Individual patient consent was not sought as this is a retrospective observational study and no patient identifiable data is reported. The study was reviewed and approved by the institutional audit department (ref 2013).

3.4 Results

3.4.1 Prospective study of antipyretic use in those admitted to PICU with infection

Data regarding the use of anti-pyretic treatment in PICU was collected in the Fever Observational study. Just over half the children received at least one anti-pyretic intervention each day, peaking on day 1 of admission. Over the 5 days, 101/140 (72.1%) received at least one anti-pyretic intervention. The commonest intervention was paracetamol – 99/101 (98%) who received an anti-pyretic intervention, received paracetamol. Non-steroidal anti-inflammatory drugs were very rarely used. External cooling was not commonly used, but this may be under-reported. The number and percentage of children receiving interventions each day is presented in Table 3.1.

Paracetamol was the commonest intervention, although it is difficult to know if fever or pain was the indication for paracetamol use. To explore this, the relationship between maximum temperature per day and the use of anti-pyretic interventions was examined. The proportion of children receiving anti-pyretic interventions above and below a range of temperatures between 36.0-39.5°C is shown in Figure 3.2. The proportion of children receiving antipyretics increases with maximum daily temperatures, with a greater increase above 37.9°C. The

portion of children receiving antipyretic interventions with maximum temperatures below 37.0°C falls steeply.

	Day 0	Day 1	Day 2	Day 3	Day 4
n	140	134	118	94	77
Paracetamol (%)	46 (32.9)	75 (55.9)	64 (54.2)	52 (55.3)	37 (48.1)
NSAID (%)	1 (0.7)	3 (2.2)	3 (2.5)	3 (3.2)	3 (3.9)
External cooling (%)	10 (7.1)	14 (10.5)	5 (4.2)	4 (4.3)	3 (3.9)
Other (%)	2 (1.4)	4 (3.0)	3 (2.5)	2 (2.1)	4 (5.2)
At least one anti-pyretic intervention	49 (35.0)	78 (58.2)	65 (55.1)	53 (56.4)	38 (49.4)

Table 3.1: The number of anti-pyretic interventions used for each day of admission.

The number of children receiving paracetamol, NSAIDs, cooling or other temperature control measures, with the percentages of the total number of children each day. The bottom row shows the number of children who received at least one anti-pyretic intervention on each day.

To further examine the relationship between temperature and paracetamol use, the cumulative distribution of anti-pyretic interventions was plotted over a range of temperatures for the first day of intervention, compared with the day prior. All interventions on day 0 had to be excluded for this analysis (Figure 3.3). There is separation between the lines: this suggests that for any given temperature between 36-40°C, a greater proportion of children had a maximum temperature below this on the day prior to receiving their first anti-pyretic intervention, compared to the day they received the intervention. From these analyses it can be inferred that temperature is related to the use of anti-pyretic interventions (largely paracetamol), even though the threshold for intervention may marginally increase above 37.8°C.

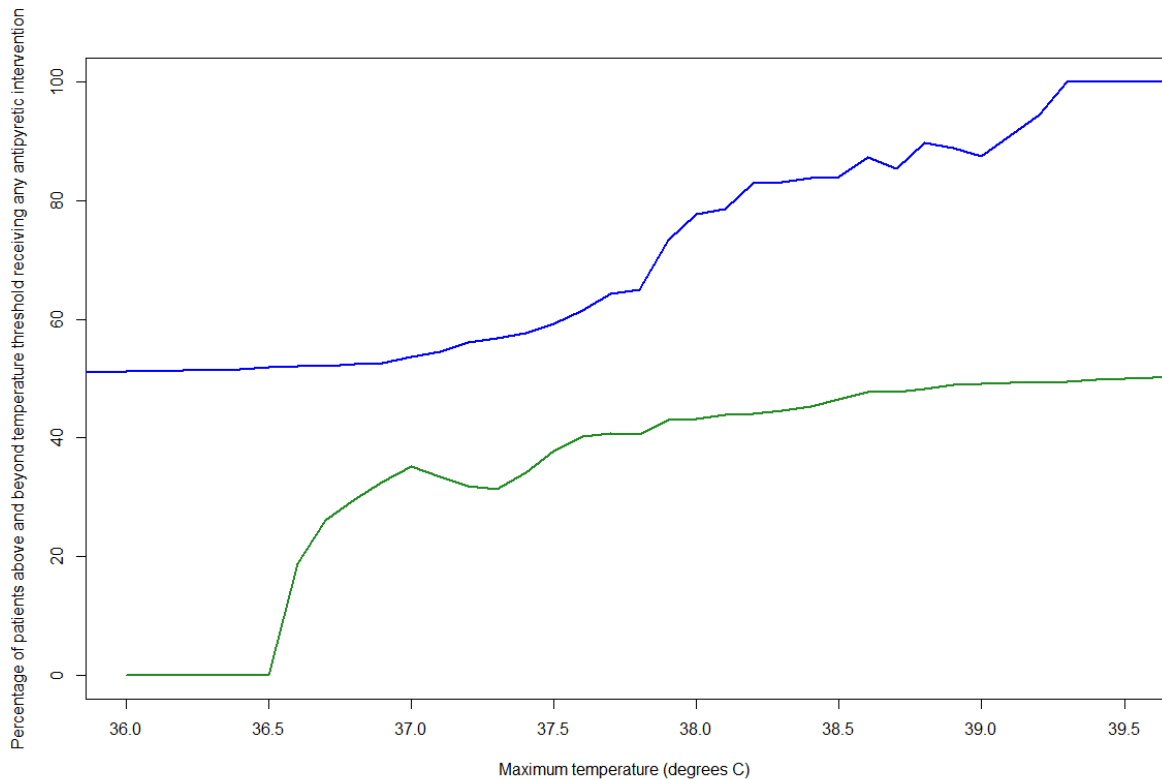


Figure 3.2: The proportion of patients receiving antipyretic intervention with a maximum temperature above (blue) or below (green) a given threshold. The proportion of patients getting anti-pyretic interventions rises, particularly as the maximum temperature rises above 37.8°C and falls if the maximum temperature is <37.0°C. All patients with maximum temperatures above 39.3°C received an antipyretic intervention; no children with a maximum temperature below 36.5°C received an antipyretic intervention.

3.4.2 The effect of paracetamol on temperature reduction in PICU

Paracetamol is the most common anti-pyretic intervention in the retrospective observational data. There were 6002 admissions across the intensive care units in unselected patients over a 40-month period. A total of 58177 paracetamol doses were administered, to 4076 children over 4681 admissions. Therefore, paracetamol was given during 4681/6002 i.e. 78% of all admissions. Most of the doses (34107/58177, 58.6%) were given in the cardiac ICU.

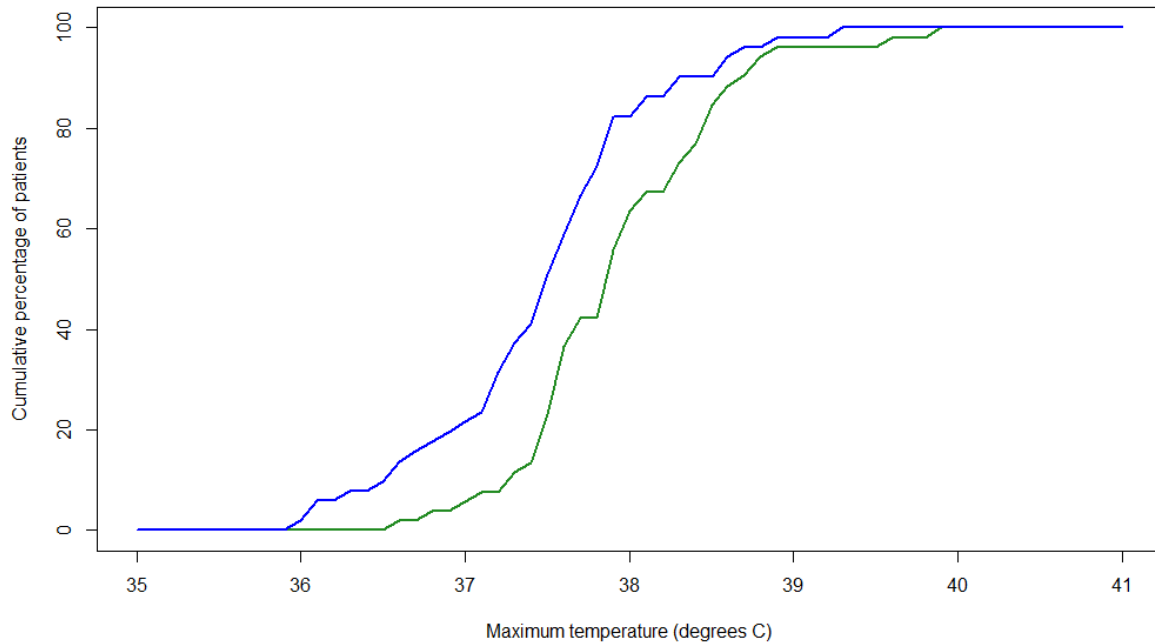


Figure 3.3: Cumulative distribution of maximum daily temperature on the day of first anti-pyretic intervention (green) and the day prior (blue). Children who received any anti-pyretic intervention on day 0 were excluded (n=51). For any given temperature in the range 36°C – 40°C, a greater proportion had a maximum temperature less than that on the day prior than on the day of the anti-pyretic intervention i.e. a rise in temperature led to the new use of an anti-pyretic intervention.

The median weight for this cohort was 7.5kg (inter-quartile range 3.7-15.8kg) and median PIM 0.017 (inter-quartile range 0.009-0.050). The patient cohort characteristics are summarised in Table 3.2.

Characteristics	Group P F (n=4849, 1463 patients)	Group F (n=6439, 1508 patients)	p-value
Weight, kg <i>median (inter-quartile range)</i>	12.8 (7.0- 27.0)	7.4 (3.4-15.5)	<2.2x10 ⁻¹⁶
PIM-score <i>median (inter-quartile range)</i>	0.028 (0.009- 0.064)	0.039 (0.015- 0.085)	<2.2x10 ⁻¹⁶
Unit			
Cardiac ICU	1620	1694	2.9x10 ⁻¹⁶
General paediatric/neonatal ICU	3229	4745	

Table 3.2: Table showing the characteristics of the patients and unit location for children with fever. Weight and Paediatric Index of Mortality (PIM-score) are expressed as median (inter-quartile range) and were compared using the Mann-Whitney U test. Those given paracetamol (Group P|F) were likely to be heavier and had a lower PIM-score compared to those not given paracetamol (Group F). A greater proportion of episodes of fever were treated with paracetamol on the cardiac ICU compared to the general paediatric and neonatal ICU (chi-squared value 67, $p=2.9 \times 10^{-16}$).

Temperature data were available for 54084 (92.9%) of the total paracetamol doses in 3779 children. Paracetamol was given when the baseline temperature (i.e. at time-point 0 or -1) was $\geq 38^{\circ}\text{C}$ in 4849/54084 doses (9.0%) in 1463 children. Two-thirds of these doses (3229/4849, 66.6%) were given on the general paediatric and neonatal ICUs. (Figure 3.4)

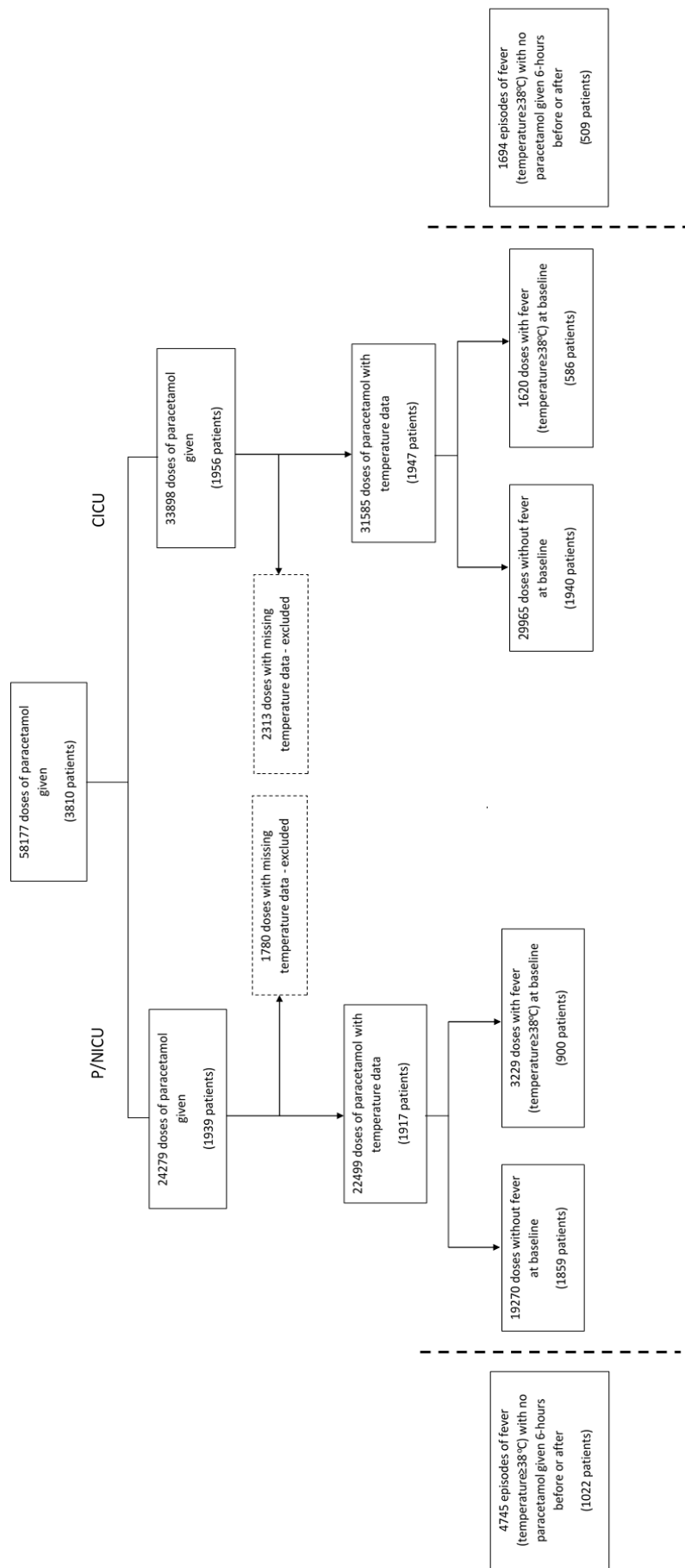


Figure 3.4: Flow diagram showing the number of paracetamol doses given in the 40-month study period, as well as the number of episodes of fever when paracetamol was not given. paracetamol doses were excluded from the analysis if no temperature were available (temperature data were only considered if the site of measurement were labelled, and the sites were not ‘peripheral’ or ‘skin’ temperatures). Fever was defined as a temperature $\geq 38^{\circ}\text{C}$. Fever at baseline was defined as a temperature $\geq 38^{\circ}\text{C}$ in the hour of or the hour before the paracetamol dose was given.

The effect of paracetamol on temperature was analysed from the retrospective electronic health record data. Figure 3.5 shows the distribution of temperature for each hour in relation to the Paracetamol dose (Group P). Following multi-level linear regression, the mean difference in temperature each hour is statistically significant: the mean decrease in temperature 4-hours post paracetamol dose was 0.11°C (95% CI 0.09-0.14°C) from baseline (time-point 0) (Table 3.3).

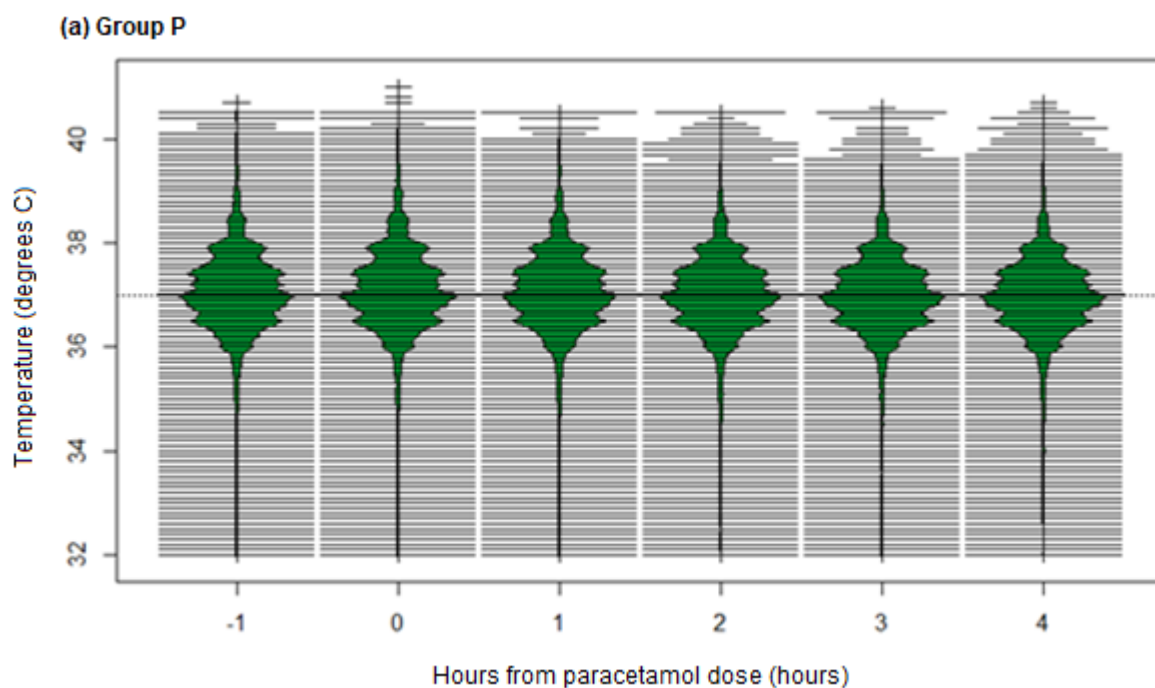
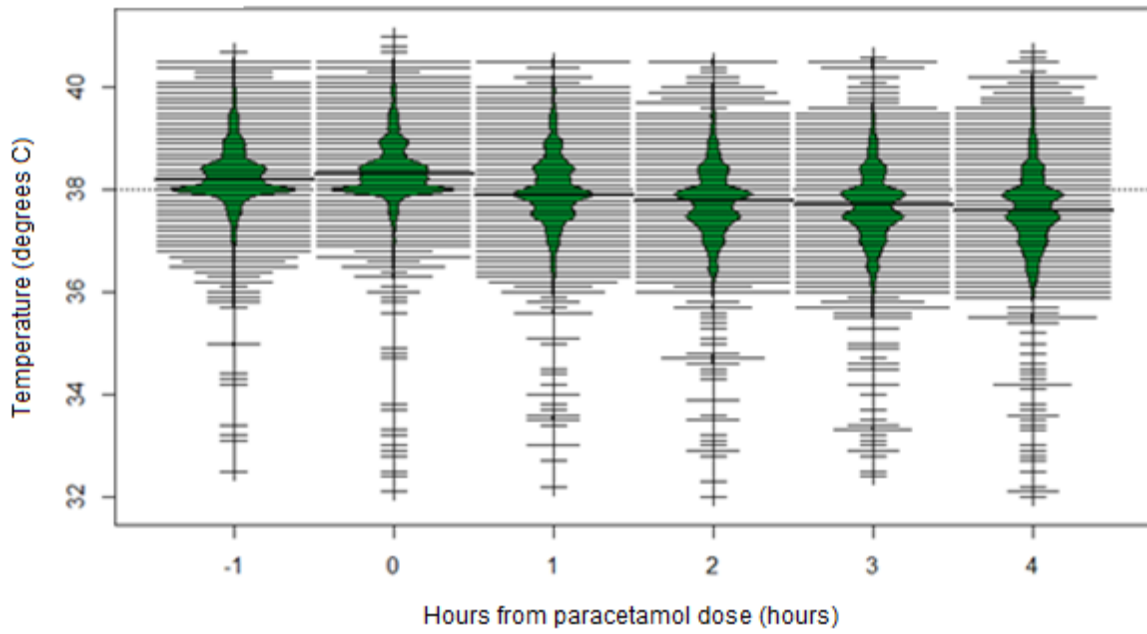
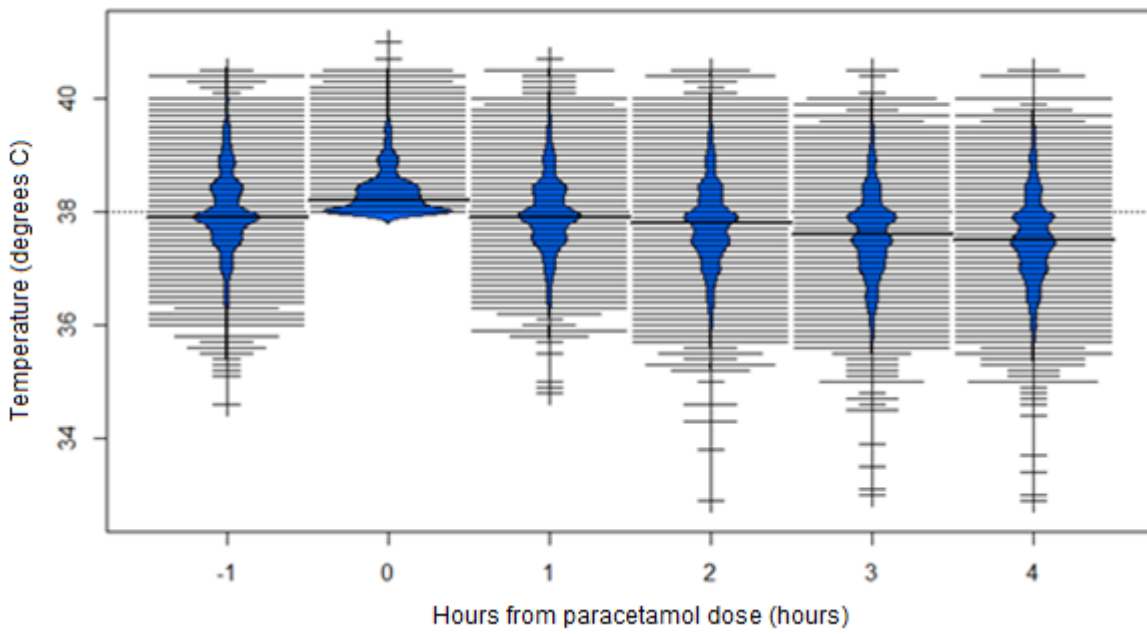


Figure 3.5: Beanplots showing temperature distribution in relation to paracetamol or fever. The panels show temperature distributions from the following groups (a) all paracetamol doses given (Group P, n=54084), (b) doses given with a fever at baseline (Group P|F, n=4849) (overleaf, top panel), and (c) episodes of fever when no paracetamol was given (Group F, n=6439) (overleaf, bottom panel). The time-points are defined in relation to the paracetamol dose, or incidence of fever in (c): time-point -1 is the hour before the paracetamol dose/fever; time-point 0 the hour of the paracetamol dose/fever; time-points 1-4 are 1 to 4 hours after the paracetamol dose or fever. Fever is defined as a temperature $\geq 38^{\circ}\text{C}$ - hence the skewed distributions for time-points -1 and 0 in (b) and time-point 0 in (c). The dotted line represents the overall median value for the population. Temperature decreases over time in both groups P|F and F.

(b) Group P|F



(c) Group F



As the temperature effect of paracetamol is due to inhibition of prostaglandin action on the hypothalamus in fever [Mirrasekhian 2017], we analysed the sub-group of doses where the baseline temperature was $\geq 38^{\circ}\text{C}$ (at time-point -1 or 0) (Group P|F). Paracetamol was given when the baseline temperature was $\geq 38^{\circ}\text{C}$ in 4849/54084 doses (9.0%) in 1463 children. The median weight for this cohort was 12.8kg (inter-quartile range 7.0-27.0kg), and median PIM score was 0.030 (inter-quartile range 0.01-0.06). Two-thirds of these doses (3229/4849, 66.6%) were given on P/NICU. Following multi-linear regression as above, the temperature decrease in fever was greater 4 hours post paracetamol dose, with a mean decrease in temperature 0.78°C (95%CI $0.74\text{-}0.82^{\circ}\text{C}$) from baseline (Table 3.3).

Effect of route of administration: The temperature effect of paracetamol was tested separately according to the route of administration. With both intravenous and enteral paracetamol doses the nadir of the temperature effect occurred 4 hours post administration (decrease in temperature 4 hours post intravenous dose 0.78°C , 95% CI $0.71\text{-}0.84^{\circ}\text{C}$; post enteral dose 0.78°C , 95% CI $0.74\text{-}0.84^{\circ}\text{C}$). The decrease in temperature however occurred sooner following intravenous administration (decrease in temperature 1-hour post intravenous dose 0.41°C , 95% CI $0.34\text{-}0.47^{\circ}\text{C}$; post enteral dose 0.37°C , 95% CI $0.32\text{-}0.42^{\circ}\text{C}$).

Effect of the dose administered: The dose of paracetamol given, expressed as milligrams per kilogram, was included in an interaction term with time in relation to the dose. When models with and without this interaction term were compared using the likelihood-ratio test, the effect of the size of dose was found to be significant (Chi-square value=37.04, p-value= 1.7×10^{-6} in Group P; chi-square value=16.57, p-value=0.01 in Group P|F).

Temperature profiles in fever without paracetamol administration: There were 6439 episodes, in 1508 children (median weight 7.4kg, inter-quartile 3.4-15.5kg; median PIM score 0.037, inter-quartile range 0.014-0.085), when a temperature of $\geq 38^{\circ}\text{C}$ was not treated with paracetamol (Group F). Three quarters of these episodes (4745/6439, 73.7%)

Time-point	Difference in temperature from time-point 0 from multi-level regression model, mean (95% confidence interval), °C		
	All paracetamol doses (P) n=54084	Paracetamol given with fever (P F) (temperature $\geq 38^{\circ}\text{C}$ at time-point 0 or -1) n=4849	No paracetamol given with fever (F) (temperature $\geq 38^{\circ}\text{C}$ at time-point 0) n=6439
-1	-0.04 (-0.07, -0.02)	-0.07 (-0.07, -0.04)	-0.38 (-0.41, -0.34)
1	-0.05 (-0.08, -0.03)	-0.38 (-0.42, -0.34)	-0.40 (-0.44, -0.36)
2	-0.10 (-0.12, -0.07)	-0.61 (-0.65, -0.57)	-0.62 (-0.65, -0.58)
3	-0.11 (-0.14, -0.09)	-0.72 (-0.76, -0.68)	-0.80 (-0.83, -0.76)
4	-0.11 (-0.14, -0.09)	-0.78 (-0.82, -0.74)	-0.88 (-0.92, -0.85)

Table 3.3: Mean temperature changes following paracetamol and fever from multi-level linear regression model. Data shown for all doses of paracetamol given (Group P), only those doses given following a fever (Group P|F), and temperature changes with a fever when no paracetamol is given (Group F). Time-points are defined in relation to the paracetamol dose: -1 = the hour before paracetamol is given, 1-4 = hours 1 to 4 after the paracetamol is given (for the group where paracetamol is not given, defined in relation to an incidence of temperature $\geq 38^{\circ}\text{C}$). Temperature changes are calculated following multi-level linear regression analysis, including weight and PIM scores as fixed effects variables, with individual patients and doses as random effects variables.

were in P/NICU. Following Mann-Whitney U Test, both weight and PIM scores were statistically significantly different between Groups P|F and F ($p\text{-value} < 2.2 \times 10^{-16}$ for both). The unit distribution (CICU versus P/NICU) was also significantly different between groups P|F and F following chi-square test ($\text{chi-squared}=67$, $p\text{-value}=2.9 \times 10^{-16}$) (Table 3.2).

Following multi-level regression as described above, the mean temperature decrease following fever without paracetamol was 0.88°C (95%CI 0.85-0.92°C).

The difference in temperature distributions following fever, with or without paracetamol treatment, was compared (Figure 3.6). When the multi-level linear regression models with or without the interaction term for paracetamol use and time were compared for children with fever, the likelihood ratio test statistic was 246.06. This suggests that the change in temperature with or without paracetamol use is significantly different (p-value $<2.2 \times 10^{-16}$). While the average temperature decrease seems to be marginally greater in Group F, the temperature is higher, for a longer duration, at baseline in the children in Group P|F.

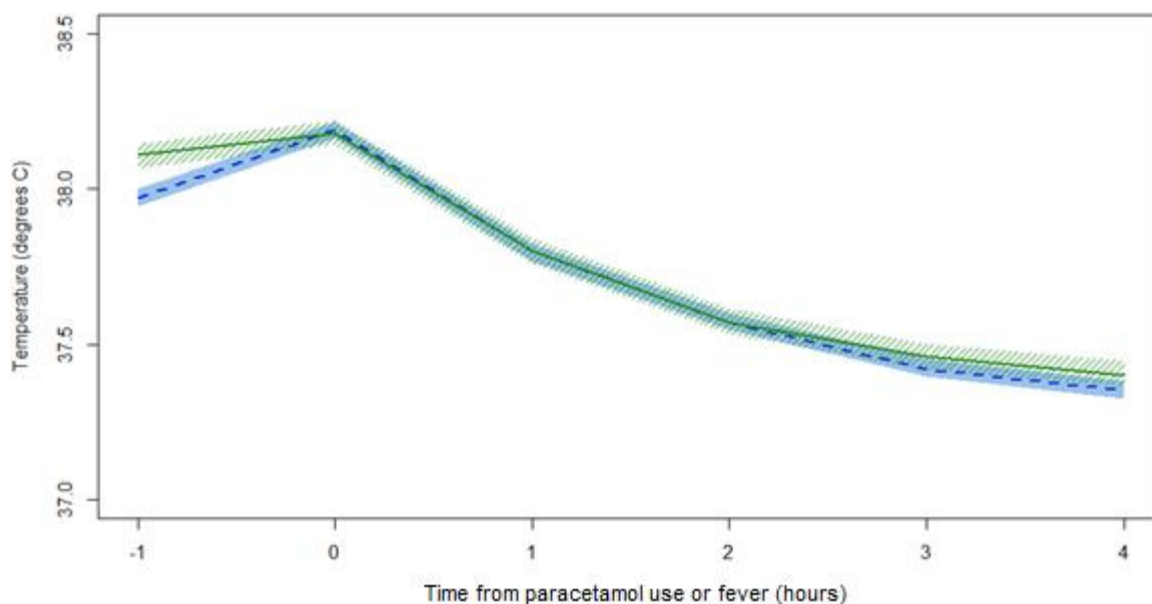


Figure 3.6: Changes in temperature in children with fever given paracetamol and not given paracetamol following multi-level linear regression modelling. The green solid line with hatched shading represents the mean and 95% confidence interval of temperatures for those given paracetamol with a fever at baseline (Group P|F). The blue dashed line with smooth shading represents the mean and 95% confidence intervals of temperatures for those with fever but not given paracetamol (Group F). The temperature falls following hour 0 in both groups, with a slightly greater drop in Group F. The temperature is elevated for longer at baseline in Group P|F compared to Group F.

3.5 Discussion

3.5.1 Summary of results

(i) The use of anti-pyretic interventions: In the population with confirmed or suspected infection, most children received at least one anti-pyretic intervention, especially on days 1-3 of admission. Paracetamol was the most commonly used of these. The use of an anti-pyretic intervention did correspond to a higher maximum temperature. However, paracetamol was also used very frequently in the unselected ICU population. In most cases this was not due to fever: more than 90% of all paracetamol doses given were done so with a baseline temperature $<38^{\circ}\text{C}$. Conversely, more instances of temperature $\geq 38^{\circ}\text{C}$ were not treated with paracetamol ($n=6439$) than were ($n=4849$).

(ii) The effect of paracetamol on temperature: Temperature decreased following paracetamol by only 0.11°C on average, and by 0.78°C (95% CI $0.74-0.82^{\circ}\text{C}$) in those with fever. However, temperature decreased over time in children with fever who did not receive paracetamol as well (by 0.88°C , 95% CI $0.85-0.92^{\circ}\text{C}$).

3.5.2 Hypothesis testing and Implications of results in critically ill children

The aim of these analyses was to understand the epidemiology of the use of anti-pyretic treatment and their effect, in particular the effect of paracetamol on temperature. In doing so the following hypotheses were tested:

Paracetamol is the most commonly used anti-pyretic treatment in PICU: Fever is short lived in children admitted to ICU. Anti-pyretics are used in over half of all children with fever. Paracetamol is by far the most common anti-pyretic treatment used ($>90\%$ anti-pyretic treatment used on all 5 days in the Fever Observational Study at Great Ormond Street Hospital), followed by external cooling. The use of external cooling however may be under-represented: although data were collected prospectively, out-of-hours data collection relied

on interventions being recorded in the electronic health record. Many external cooling interventions such as use of fans or ice-packs may be poorly recorded, as they are often used for short periods of time.

Nevertheless, paracetamol is used most frequently. The use of paracetamol is not restricted to children with fever – only 9% of paracetamol doses were given with a temperature $\geq 38^{\circ}\text{C}$ in the hour before or the hour of receiving paracetamol. In the retrospective analysis of paracetamol use, a larger number of children with fever did not receive paracetamol than those who did. This is particularly surprising given how commonly paracetamol was used overall i.e. in just under 80% of all admissions. There is however evidence from the prospective study that the use of anti-pyretic interventions, and therefore paracetamol, was linked to maximum temperature. The use of anti-pyretic interventions increased as the maximum temperature approached 38.0°C and fell if the maximum temperature was $<37.0^{\circ}\text{C}$. Similarly, the maximum temperature was lower on the day before compared to the first day they received an anti-pyretic.

The use of paracetamol as the most commonly used anti-pyretic agent is reflective of the national cohort in the Fever Observational Study [full report accessed at <https://njl-admin.nihr.ac.uk/document/download/2009621>]. Treatment of fever occurred in 54% of children. Of 984 children who received any anti-pyretic treatment on day 1 of PICU admission, 934 (94.9%) received paracetamol. There was a smoother temperature relationship with anti-pyretic use in the national cohort compared to Great Ormond Street Hospital: the proportion receiving anti-pyretic use increased continuously with increasing maximum temperatures (Figure 3.7). This is likely to be due to a larger sample, reflecting a greater variation in practice i.e. different temperature thresholds at which to use paracetamol.

Children with fever were more likely to be given paracetamol if they were on cardiac ICU. This may be due to 2 reasons: (i) children in cardiac ICU are more likely to receive paracetamol routinely for post-operative analgesia, and (ii) temperature is managed more

aggressively post bypass to reduce the risk of tachy-arrhythmias and reduce the temperature induced increase in heart rate to improve diastolic filling and stroke volume. This is consistent with the reduced variation in temperature seen in children on cardiac ICU, especially after 24 hours.

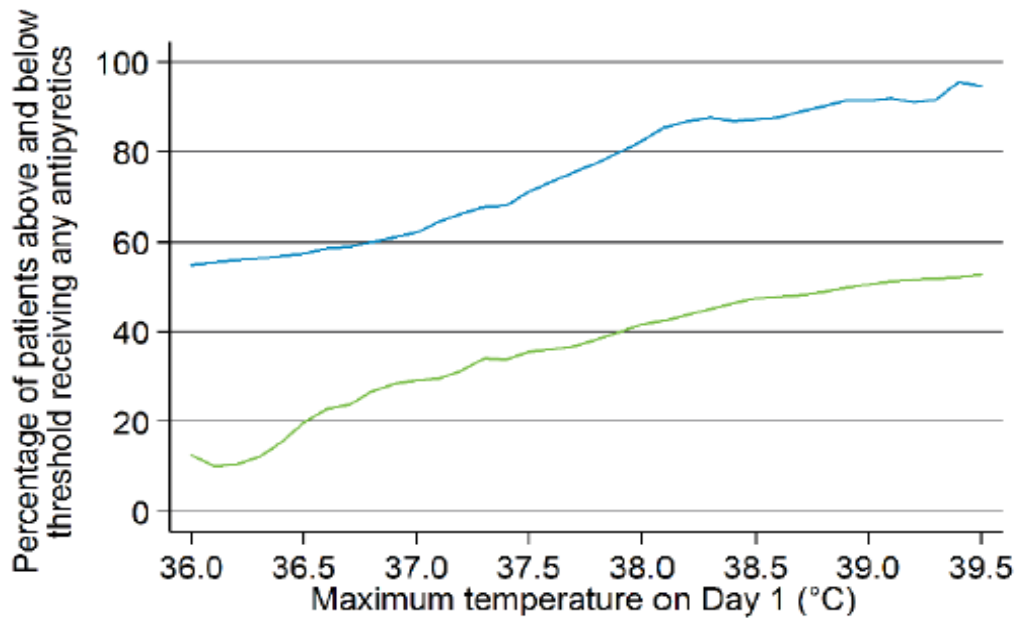


Figure 3.7: Data from the national cohort of the Fever Observational Study (22 sites) on the threshold for using paracetamol on day 1 of admission. The proportion of children receiving paracetamol above (blue line) and below (green line) a temperature threshold rises across the temperature range. This is in similar to Figure 3.2, which shows data from Great Ormond Street Hospital only, albeit for all 5 days of admission (rather than day 1) [copied with permission Peters 2019a].

Paracetamol is associated with a temperature reduction by $\geq 0.5^{\circ}\text{C}$ but may not compare favourably to use of no paracetamol: The data demonstrate that while the temperature change by 0.11°C post-paracetamol administration (Group P) is statistically significant, this is unlikely to be clinically significant – individual body temperatures have been described to show diurnal variation greater than this [Mackowiak 1992]. However, when paracetamol is given with a fever (Group P|F), the mean reduction in temperature 4-hours post paracetamol is 0.78°C . Enteral and intravenous doses had similar effect sizes,

although the decrease in temperature occurred sooner following intravenous administration. The size of the dose had a significant impact on the change in temperature.

In the group of children who had fever but were not given paracetamol (Group F), the temperature decrease was similar, if not slightly greater (mean reduction in temperature of 0.88°C). However, the indication for giving paracetamol (or not giving paracetamol) may be relevant. In a retrospective observational study, this is difficult to determine. Paracetamol is used commonly but only 9.0% of doses were given with a fever. More children with a fever were not given paracetamol. Although in a previous survey of practice within the UK (including staff from our centre) staff reported to treat a temperature of $\geq 38^{\circ}\text{C}$ [Brick 2017], it is possible that the threshold temperature for giving paracetamol may be context dependent. While most children with fever got some anti-pyretic intervention in the Fever Observational Study, over 40% did not. Children with fever who received paracetamol weighed more and had lower PIM scores, compared to those who did not receive paracetamol. It is possible that the temperature changes in children in Group F reflect an increased lability in temperature in smaller, sicker children. However, weight and PIM were both included in the multi-variate models: despite this, there was a significant difference in the temperature profiles between groups F and P|F.

These results suggest that the temperature effect of paracetamol may be more modest than previously reported in children (0.78°C versus $>1^{\circ}\text{C}$). This should be considered when designing a trial to demonstrate the temperature effects of paracetamol in children on ICU. However, similar retrospective study in adults showed similar results [Greenberg 2010], only for subsequent randomised trials to suggest a greater effect of paracetamol on temperature [Tsaganos 2017; Schell-Chaple 2017].

3.5.3 Limitations

There are several limitations with the studies presented, which need to be considered when interpreting the results.

- 1) The studies present data from a single centre. The prospective data presented are from a single centre. The use of paracetamol is very high within Great Ormond Street with 78% of all children receiving paracetamol at some point in their admission. This said, no children with a maximum temperature $<36.5^{\circ}\text{C}$ were given paracetamol at Great Ormond Street Hospital (there were 6 children in the cohort with a maximum daily temperature $<36.5^{\circ}\text{C}$). The use of paracetamol also increases with temperature, reflecting national results (Figs 3.2 and 3.3)
- 2) The threshold at which anti-pyretic interventions were used was indirectly inferred from maximum temperature data in the prospective observational study. This is difficult to do given the frequent use of paracetamol, although the likelihood of paracetamol use increases if the maximum temperature was $>37.8^{\circ}\text{C}$. Ideally the indication for paracetamol use could have been collected. In the retrospective study, data on the temperature in the hour before or the hour of paracetamol administration (time-points -1 and 0) were collected. These are hourly values and could have been measured at any time during the hour. It is possible that paracetamol was given before the temperature was taken at time-point 0.
- 3) As in Chapter 2, data on the mode and site of temperature measurement were not collected in the prospective study. This could affect the different thresholds of fever treatment on different days within the same patient. In the retrospective study axillary and tympanic temperature was considered as equivalent to central temperatures. It is less likely that the mode of temperature measurement would have changed for a large number of cases within the 6-hour window considered in the retrospective study i.e. if an axillary temperature was taken at time-point 0 it is unlikely the next measurement was a central temperature and vice versa. A post-hoc analysis of the

subgroup with only core temperature measurements (oesophageal, rectal or bladder) showed a decrease in temperature of 0.72°C (95% CI 0.64-0.80°C) 4 hours post paracetamol in Group P|F, and 0.89°C (95% CI 0.80-0.98°C) 4 hours post fever in Group F.

- 4) A retrospective study of paracetamol effect cannot fully account for selection bias, i.e. paracetamol given for analgesia, or reason behind not giving paracetamol. This study could be conducted prospectively to reduce selection and observer bias. However, one of the strengths of the retrospective study is the number of doses (or episodes of fever) that can be studied – this can type I error even accounting for biases.
- 5) In measuring the effect of paracetamol on temperature, data on other interventions such as environmental cooling were not collected. It is possible that paracetamol was given only if other measures were unsuccessful in decreasing temperature e.g. fan therapy or surface cooling. To this extent, it is notable that the temperatures are higher at baseline, for longer, in group P|F compared to Group F: nearly 80% of children have fever at time-point -1 in Group P|F, compared to just fewer than 50% in Group F (Figure 3.6). This could be a definitional artefact: in group P|F, fever was defined as a temperature $\geq 38^{\circ}\text{C}$ in the hour of the paracetamol dose (time-point 0), or the hour before (time-point -1). Children in group F were identified by the presence of a temperature $\geq 38^{\circ}\text{C}$, which was labelled time-point 0 (some children had a temperature $\geq 38^{\circ}\text{C}$ at time point -1 in Group F but they had paracetamol in the 6 hours prior to this time). To test this further, fever in group P|F was redefined as only those with a temperature $\geq 38^{\circ}\text{C}$ at time-point 0 and the analysis was repeated. The median temperature at time-point -1 was 38.0, and the temperature distribution remained different from those not given paracetamol (comparing models as previously described, the likelihood ratio test statistic was 68.72, $p < 7.5 \times 10^{-13}$). It is possible that paracetamol is more likely to be administered if fever is persistent beyond a single reading, with or without other temperature control mechanisms.

- 6) The inclusion of neonates within the retrospective study may have also altered the temperature changes. Neonates, particularly those with low-birth weight or premature, have poor thermoregulatory mechanisms, and temperatures may reflect incubator temperatures. This, in particular, could explain some of the temperature reduction seen in group F who were not treated by paracetamol. In these cases, the temperature-based definition of fever may not be adequate – they may not have an altered temperature set-point. Weight was a significantly different variable on univariable analysis between groups P|F and F – those in group F weighed less. However, to mitigate this, weight was included within the multi-variable model. Also, as evident from the unselected population study in Chapter 2, the number of children who were extremely premature (i.e. <27 weeks) at the time of admission to Great Ormond Street Hospital was very small. This group would be at the greatest risk of immature thermoregulation, and it is unlikely that this population could fully account for the effect seen in Group F.
- 7) Paracetamol may have been given prior to admission, which may not have been accounted for in the retrospective study of the paracetamol effect on temperature. However, only 706/6441 (11.0%) episodes of fever in Group F in the retrospective analysis were within the first 6 hours of admission.

3.6 Conclusions

Anti-pyretic interventions are common in PICU – over 50% of unplanned admission with infection receive them. Paracetamol is by far the most commonly used – although not always used in children with fever, the use of paracetamol was associated with temperature.

These results suggest that in current practice fever treatment is common. This may be of benefit if fever leads to an imbalance between oxygen consumption and delivery. Alternatively, if fever is beneficial, and there is no oxygen debt associated with it, then

treating fever may not be justified. In order to explore this further it is important to evaluate the changes in oxygen consumption with fever in children on PICU.

Chapter 4 Energy expenditure during fever and following treatment

4.1 Introduction

Fever is an energy-hungry process. This is expected: heat implies the dissipation of energy. The degree of increase in energy expenditure to generate a fever has been estimated to be potentially up to 7-12.5% per 1°C rise in temperature in healthy humans [Altschule 1945; Shapiro 1966; Manthous 1995]. In critically ill adults, energy expenditure increases by 15-18% with fever, equating to approximately 10-13% increase per °C rise in body temperature [Manthous 1995; Hata 2008; Bruder 1998; Gozzoli 2004]. If, in critical illness, this increase in oxygen consumption cannot be matched by oxygen delivery, then an oxygen debt could result.

There is reason to believe that changes in oxygen consumption with fever in children may not be the same as in adults. Both energy metabolism and body composition change through mammalian development. The energy requirement of the developing infant brain is 3-fold higher than that of an adult human [Jones 1979]. Babies are born with a high percentage of fat, which declines through childhood after a peak in late infancy (perhaps a reflection of the energy demands of development) [Kuzawa 1998]. A high proportion of brown adipose tissue is available for heat production in neonates and infants compared to adults [Heaton 1972]. Children have a larger body surface area to weight ratio. This means they are more prone to surface heat loss. Conversely, they may be able to preserve heat and therefore raise their temperature by a greater degree through peripheral vasoconstriction. Notably, Hull and McIntyre were unable to consistently demonstrate an increase in energy expenditure in children with fever, unlike the evidence in adults.

Neonates are equally likely to show a hypothermic response in sepsis as they are fever [Hofer 2012]. This may be due to an inability to mount a fever response, or an inability to produce the thermoregulatory changes required (i.e. to generate and/or conserve heat). The latter has been demonstrated in animals – sepsis induced cytokines can lead to an impairment of mitochondrial oxidative function in rats (which could be reversed by glutamine), leading to problems with heat generation [Eaton 2003]. If the lack of energy, or an inability to use energy, determines whether a fever response is mounted or not, then in states of severe shock, hypothermia may prevail over a febrile response. This leads to a question about whether the body is able to prioritise energy expenditure according to functional value – i.e. does the body generate a fever only if it can afford to do so? This fits within the ‘Central Governor Hypothesis’ – that a central regulator determines which physiological processes should be prioritised or can be afforded to provide a survival advantage [Humphrey 2012]. No such single regulator has been uncovered. If so, then the priority given to fever may determine its importance to survival.

In this chapter, I attempt to quantify oxygen consumption and estimate energy expenditure during fever in children admitted to PICU, using indirect calorimetry. In order to understand how much energy is used to generate a fever, I aimed to measure energy expenditure before, during and after fever. This will help with the understanding of whether the generation of a fever comes at an energy demand greater than can be met by an increase in oxygen delivery.

4.2 Aims and hypothesis

Aims of the study:

To quantify the changes in oxygen and energy consumption in critically ill children with fever.

Hypothesis:

Null hypothesis: Fever will be associated with <10% difference of baseline energy expenditure per 1°C change in temperature in critically ill children ventilated on the intensive care unit

Alternative hypothesis: Fever will be associated with a ≥10% difference of baseline energy expenditure per 1°C change in temperature

4.3 Methods

Study design and setting: This was a prospective observational cohort study using indirect calorimetry to measure oxygen consumption in critically ill children admitted to PICU at Great Ormond Street Hospital.

Participants: Children admitted to the paediatric intensive care unit at Great Ormond Street Hospital between November 2016 to November 2018 (24 months) with suspected infection, following trauma or major surgery, who are likely to develop a fever.

Eligibility criteria:

Inclusion criteria

- Children >10kg (The MGC Diagnostics – formerly Medgraphics - Ultima CCM calorimeter has been used safely in children as low as 10kg)
- Children with suspected infection, following trauma, or post-major surgery

Exclusion criteria

- Children post brain injury
- Children with refractory status epilepticus
- Children post cardiac arrest

- Children post cardiac bypass
- Children with cardiac arrhythmias
- Children not invasively ventilated
- Children with a greater than 5% leak around their endotracheal tube (measured from ventilator inspired and expired tidal volumes)
- Children with a fraction of inspired oxygen (FiO_2)>0.60

Children with brain injury, either traumatic injury or post hypoxia, were excluded given some evidence of worsening outcomes with fever [Badjatia 2009; Bohman 2014]. Children with refractory status epilepticus were excluded, as higher temperatures can reduce the seizure threshold [Shinnar 2003; Verity 1991]. Children post bypass and with arrhythmias were excluded as fever can cause tachycardia and increase arrhythmogenicity [Beaulnes 1957]. Children had to be invasively ventilated with minimal leak to be able to get accurate calorimetry readings (although can fit a non-invasive mask or mouth-piece, children on PICU are unlikely to tolerate this). The FiO_2 had to be less than 0.60 as above this value the inspired and expired oxygen measurements are inaccurate.

Study outcomes

Primary outcome: Change in energy expenditure per °C change in temperature

Secondary outcome: Change in oxygen consumption, carbon dioxide production and respiratory quotient per °C change in temperature. Change in oxygen extraction ratio (ratio of oxygen consumption to oxygen delivery) per degree Centigrade change in temperature using oxygen delivery data from the LiDCOrapid (LIDCO Ltd, UK) cardiac output monitor if in place.

Study procedures:

Screening and Recruitment

- All paediatric intensive care patients were screened each morning for weight, ventilation status and likelihood of developing a fever
- If appropriate, the clinical team on call were asked if calorimetry was feasible and appropriate for the patient
- If the clinical team felt this is appropriate, then the study was explained to families along with a parental information sheets and written informed consent was sought.
-

Study procedure

1. Once consented, calorimetry was undertaken using the MGC Diagnostics Ultima CCM (Minnesota, USA) (Figure 4.1). This was done in the following steps:
 - a. Assessment of the patient for stability:
 - i. no change in inotropes (dopamine, adrenaline, noradrenaline, vasopressin, milrinone, dobutamine) in previous hour
 - ii. no change in ventilator settings including FiO_2 in the previous hour
 - iii. $FiO_2 < 0.6$
 - iv. tidal volume ventilation > 60 ml (ideally greater than 100ml)
 - v. air leak around endotracheal tube (ETT) $< 5\%$
 - vi. no increases in sedation in past hour

- vii. no major stimulatory events (physiotherapy, turning, suction) in the previous hour

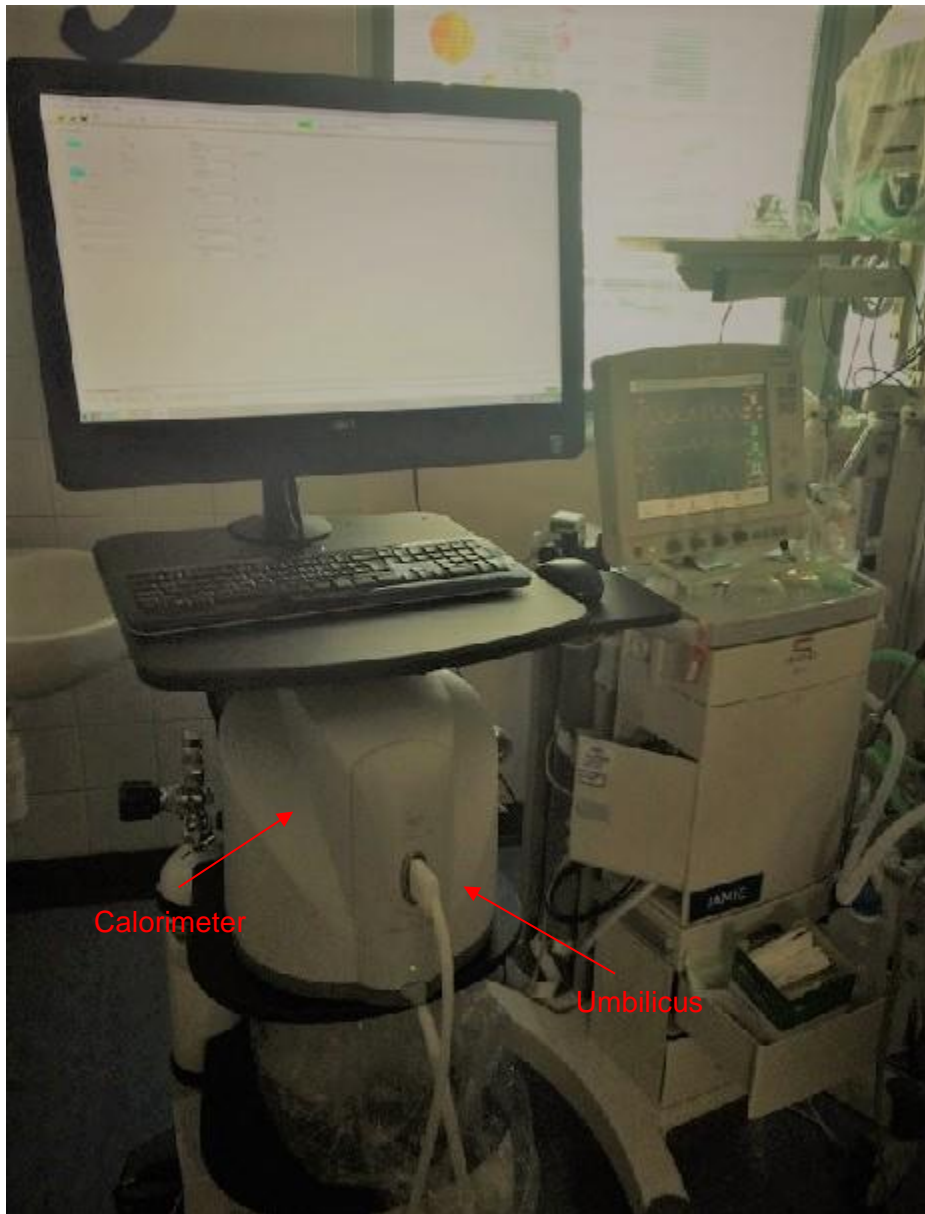


Figure 4.1: The MGC Diagnostics Ultima CCM Calorimeter. The MGC Diagnostics Ultima Calorimeter in a patient bed space prior to use. The umbilicus is inserted into the ventilator circuit at the endotracheal tube end, which samples the inspiratory and expiratory gas. The readings are continuously displayed on the screen.

- b. Recording of demographic data, ventilator settings and measurements, calorie intake, heart rate, blood pressure, cardiac index (if monitored), drug

infusion rates, use of paralysis, COMFORT score to assess sedation [Ambuel 1992], temperature

- c. If the patient was stable, then the gas sampler was attached to the end of the endotracheal tube (ETT) to the ventilator end of capnograph/flow sensor.
 - d. Measurement was stopped immediately if any deterioration in ventilation with measurement
 - e. After 30 minutes, or sooner if steady state is reached, i.e. at least 5 consecutive minutes of less than 10% variation in O₂ and CO₂ concentrations (expressed as energy expenditure (EE) covariance by the indirect calorimeter), the measurement was stopped. This was the baseline measurement.
2. If the patient developed a temperature >38°C (axillary or central measurement) within the 4 hours of the baseline measurement, step 4 a-d were repeated. The calorimeter was left on the patient for continuous data collection until the temperature fell below 38°C (with or without anti-pyretic treatment), unless the patient needed an intervention, or the measurement of inspired and expired gases became unreliable (energy expenditure co-variate >10%)
 3. If continuous measurement was not possible because of clinical needs (nursing or medical request, need for suctioning, patient instability), a 3rd measurement was taken once the temperature decreased below 38°C within 4 hours of the previous measurement (Figure 4.2)

If the patient was febrile at screening, measurement was started at step 2

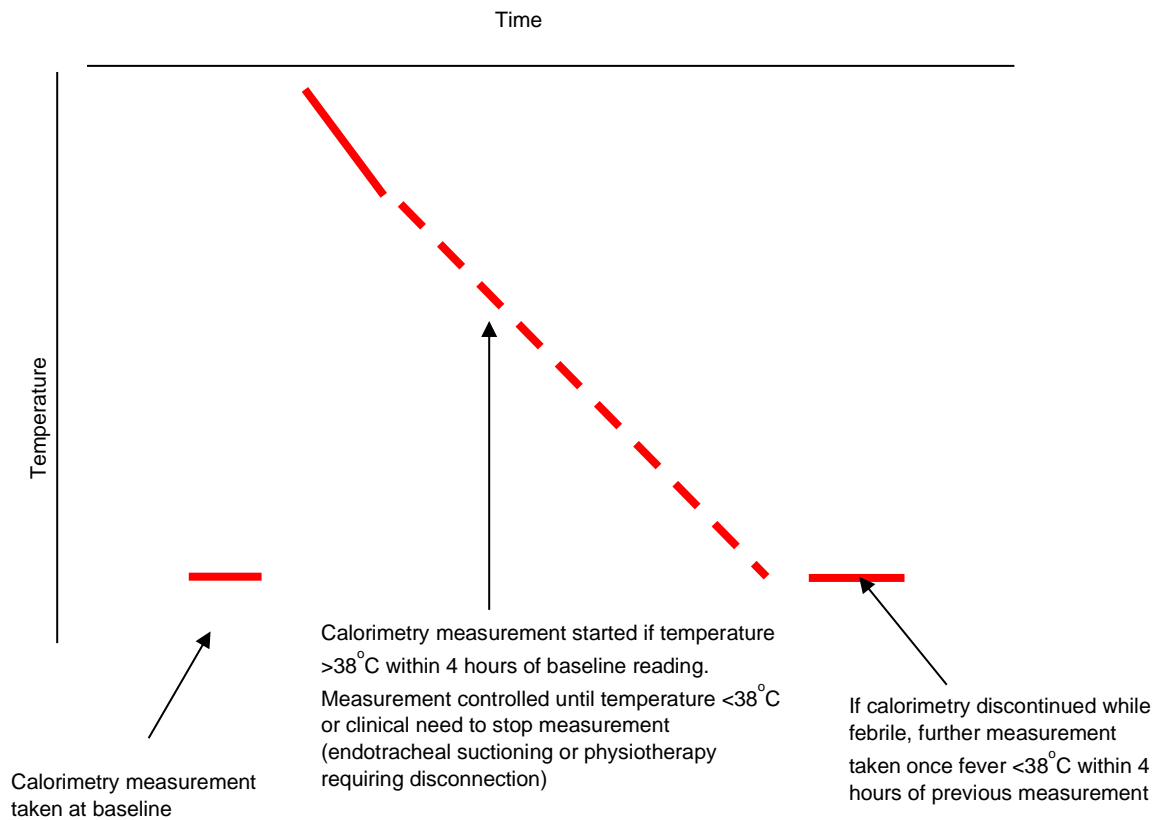


Figure 4.2: Schematic showing plan for calorimetry measurements in children post-recruitment. Baseline measurement to be taken in all eligible children with likelihood of fever. Second measurement to be started if fever within the following 4 hours, with continuous measurement until temperature $<38^{\circ}\text{C}$ (with or without paracetamol). If continuous calorimetry is not possible, then plan to take a third measurement when temperature $<38^{\circ}\text{C}$.

Patient safety: The calorimeter samples air from the ventilator circuit at a constant rate of 125ml/min. This potentially could affect ventilation in patients with very low tidal volumes. The MGC Diagnostics Ultima CCM is licensed for use for patients with tidal volumes of 100ml or more. This will usually equate to children around 15kg. However, our collaborators in Addenbrooke's Hospital, Cambridge (Dr N Pathan) had used the MGC Diagnostics Ultima CCM in children down to 10kg without an detectable safety concerns – therefore this was the

limit used, given that >50% of the PICU population are under 2 years of age [PICANET 2018].

During measurement the child's respiratory rate, oxygen saturation levels and end tidal CO₂ were monitored closely - calorimetry was discontinued if any of these values changed significantly, as judged by the bedside nurse or myself.

Data collection: Data were collected for

- Demographic data (ID, weight, height, age, sex, diagnosis)
- Oxygen consumption (VO₂) and carbon dioxide production (VCO₂); respiratory quotient (RQ); energy expenditure (as calculated by the MGC Diagnostics Ultima CCM calorimeter using the Weir equation)
- Physiological variables (heart rate, blood pressure)
- If cardiac output monitor in place: stroke volume and cardiac index (as measured by LiDCORapid, LIDCO Ltd, UK) and latest haemoglobin
- COMFORT or sedation score
- Inotrope infusion doses
- Paralysis (yes/no)
- Temperature
- Nutritional intake in last 24 hours or since admission

Oxygen consumption and carbon dioxide production were indexed for weight as described by McIntyre and Hull [McIntyre 1996]. To index the energy expenditure for children, it was expressed as the percentage of energy expenditure predicted by the Schofield equation using weight and height [Schofield 1985]

$$\text{Predicted energy expenditure} = (84 \times \text{weight in kg}) + (4.7 \times \text{height in cm}) + 200$$

Data were collected at the start of each recording and then at 15, 30, 45 minutes past the hour and every hour. Calorimetry data are recorded every 30 seconds by the MGC Diagnostics Ultima CCM calorimeter. For the first data-point (i.e. at the start of calorimetry), mean values for VO₂, VCO₂, RQ and EE for the first 5 minutes are used. For subsequent data-points, mean data over a 10-minute period were used: for example, for the data point taken at 15:15, mean data from 15:10-15:20 were used to represent the calorimetry values at 15:15.

If cardiac monitoring was in place, continuous data (as recorded by the LiDCOrapid) were used to calculate oxygen delivery.

Bias: Bias was minimised by collecting data on confounders. However, eligibility was not limited to children with single diagnoses, which increased the heterogeneity of energy expenditure amongst the sample. As measurements were being compared before, during and after fever, it was assumed that diagnosis would not change the amount of oxygen consumed/energy used to generate a fever. Similarly, the time from admission was not considered, assuming this did not affect energy expenditure in fever.

Sample size: Not enough prior data existed to estimate the standard deviation of energy expenditure using the MGC Diagnostics Ultima CCM calorimeter in critically ill children over the time period to be measured. However, a standard deviation of 10% has been observed in critically ill children by groups who have measured energy expenditure in large numbers of children (personal communication from Dr R Meyer, Imperial College, London). Based on this, for a 10% effect size, with a one-tailed α of 0.05 and $(1-\beta)$ of 0.8, a sample size of 10 children would be needed, provided a 1°C difference of temperature is seen. An analysis of temperature change following over 5000 doses of paracetamol in febrile children suggested a mean reduction of temperature by 0.7°C. Based on this therefore the aim was to recruit $10 \times 1/0.7 = 15$ patients

However, this cohort would have several confounders which needed to be taken into account by multi-variable analysis. Therefore, the aim was to recruit at least 15 children with measurements before-during and after fever. To do so, an initial 12-month recruitment period was anticipated.

Data analysis: Uni-variable analysis was undertaken by subtracting the energy expenditure at baseline (and after fever recedes from the energy expenditure) during the maximum temperature during fever, divided by the change in temperature to measure the energy expenditure per 1° C change in temperature.

Multi-variable analysis using a multi-level regression model was used with

- Change in energy expenditure as the outcome variable
- Patient ID as the random effect variable as different children will have different changes in energy expenditure over a period of time based on other illness and treatment variables
- Temperature, COMFORT score, vasoactive inotrope score, heart rate, blood pressure as fixed effect variables. The use of neuromuscular blockade was expressed as a binary categorical variable. It was expected that all of these would have fixed effects on energy expenditure regardless of differences between individual patients.

This was repeated with oxygen consumption, carbon dioxide production and respiratory quotient. Measured values, rather than measurements indexed for weight (and height) were used in the multi-variable analysis.

If cardiac output monitoring is in place, then the oxygen extraction can be calculated as VO_2/DO_2 , where,

$DO_2 = \{ \text{cardiac index} \times ((\text{oxygen saturation of haemoglobin} \times \text{haemoglobin concentration}) + 0.0031 \times \text{partial pressure of oxygen}) \}$

and VO₂ is measured from the calorimeter

Consent: Informed consent was sought from parents/guardians with parental responsibility prior to measurement. Paper consent forms were stored securely in the Great Ormond Street Critical Care Research Office.

Ethical considerations: The study was conducted in accordance to Good Clinical Practice principles and the principles of the Declaration of Helsinki. Ethical approval was granted by the NHS Health Research Authority (IRAS Project ID 209010).

4.4 Results

4.4.1 Screening and recruitment Screening began on 16th November 2016. Over the next 12-month period, 927 children were admitted to the PICU (including NICU). Of these, 394 (42.5%) were greater than 10kg at admission. Two hundred and ninety-five (74.9%) of these children were invasively ventilated during their stay. There were 2992 episodes of fever (temperature > 38°C) in 171 children.

Only 17 parents were approached for consent, either due to children meeting exclusion criteria or the fever occurring out of working hours. Priority was also given to contemporaneous interventional trials - both Oxy-PICU (<https://www.icnarc.org/Our-Research/Studies/Oxy-Picu>) and Fever (<https://www.icnarc.org/Our-Research/Studies/Fever>) feasibility trials occurred during the recruitment period. Twelve families consented for recruitment (Figure 4.3).

Given the low numbers, recruitment was continued for a further 12-month period, without daily screening (opportunistic recruitment). No children were recruited during this period.

Data were available from one patient who underwent calorimetry for clinical reasons, without prior consent – these data were not included.

Only one patient had a calorimetry measurement at baseline followed by a measurement during fever and two patients had measurements during fever and defervescence thereafter. Therefore, the hypothesis that energy expenditure increases by 10% from baseline during fever could not be accurately tested. Also, no patients who underwent calorimetry had cardiac monitoring ongoing, so no data on oxygen extraction was available. This was mainly because most children did not have arterial catheters in situ; in those who did, calorimetry was prioritised and set up of cardiac monitoring was not possible within the same time frame.

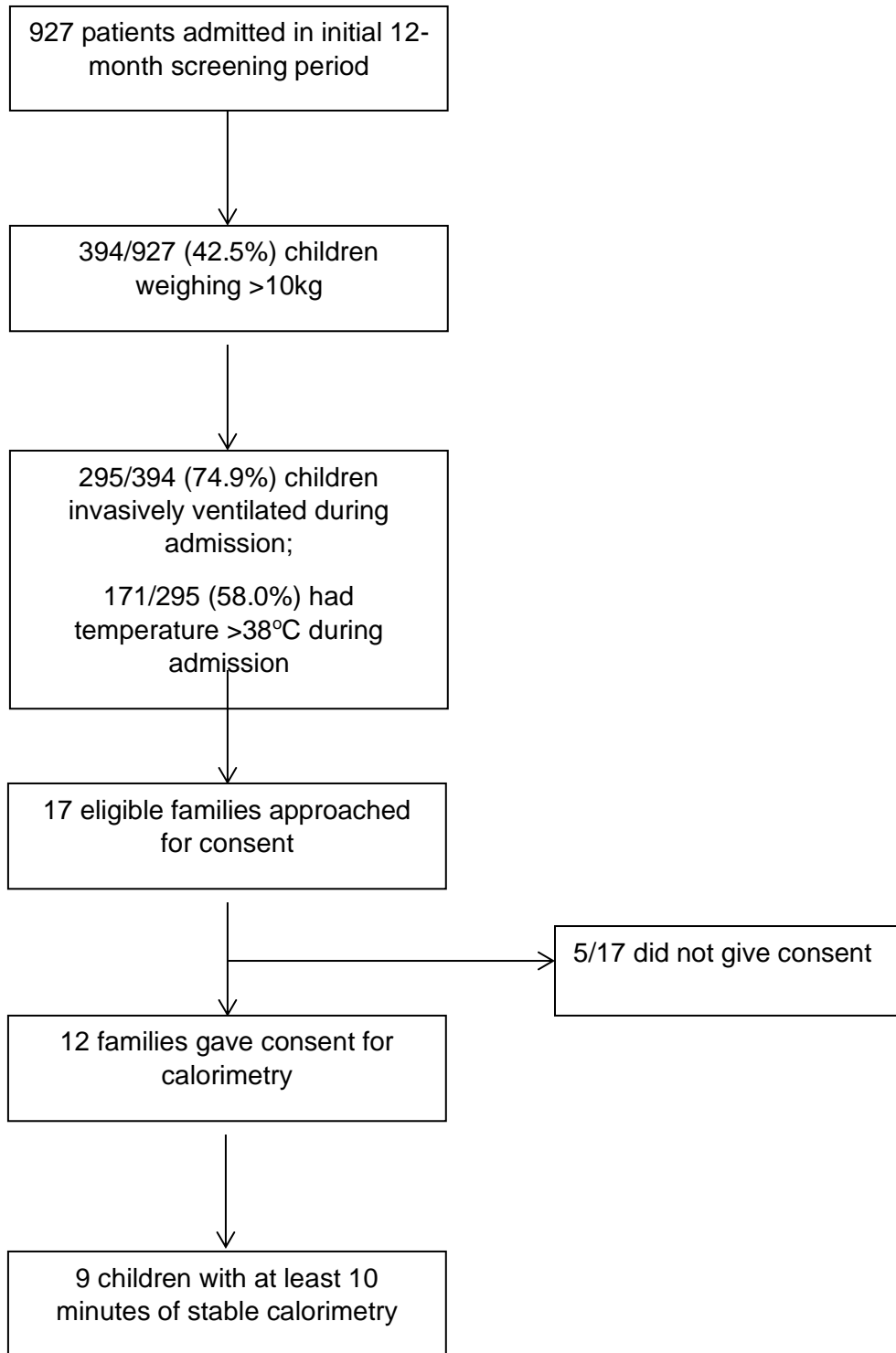


Figure 4.3: Flow diagram showing recruitment of children for calorimetry over a 12-month period. Following poor recruitment, opportunistic recruitment was extended by a further 12 months, without routine screening. Five families declined consent: although not formally sought, most families declined consent as they felt it would be “too much for their child” while critically unwell.

However, the collected data were explored to gain some understanding of possible changes in energy expenditure with temperature.

4.4.2 Description of cases

Case 1:

This 11-year old girl was admitted with septic shock (culture negative) with a background of severe constipation with previous colostomy. She had fever from day 5, with persistent fever on day 6. Calorimetry measurement was started when the temperature was 38.5°C. Her temperature rose to 38.8°C over the 72-minute measurement, after the which patient needed airway suctioning. A second measurement was taken 1-hour post-suctioning, after paracetamol was given (temperature decreased from 38.9 to 38.6°C over 2-hour period). However, the EE covariance was >10% during this period, and these data were not used. The patient was on milrinone at 0.3mcg/kg/min. She was sedated with morphine and midazolam and did not receive neuro-muscular blockade. Paracetamol had been given 2 hours prior to the first measurement.

Case 2:

This 13-month old boy with cystic fibrosis was admitted with pneumonia. No viruses were detected on NPA or bacteria on tracheal aspirates. He was on antibiotics prior to admission. A baseline measurement was taken on day of admission. However, there was no fever throughout his admission. He was sedated with morphine and midazolam but not neuro-muscular blocked. He was enterally fed. No paracetamol had been given prior to the measurement during this admission.

Case 3:

This 4-year old boy was admitted with status asthmaticus. He developed fever on day 1 of admission. RSV A was isolated from his naso-pharyngeal aspirate. Calorimetry was undertaken on day 2 during fever defervescence, capturing a decrease in temperature from

37.8°C to 37.5°C over 1 hour. He was on noradrenaline at constant dose of 0.08 mcg/kg/min during the measurement. He was sedated on midazolam with no neuro-muscular blockade. Paracetamol had been given 6 hours before calorimetry had started.

Case 4:

This 15-year old girl with a chromosome 4 deletion, global developmental delay and a neuro-muscular scoliosis was admitted with suspected aspiration pneumonia. She had a fever on day 1 of admission. A baseline measurement was taken on day 1 for 30 min with temperature 37.6°C when she was on no vaso-active drugs, sedated with morphine and propofol and not receiving neuro-muscular blockade. Fever developed within 2 hours of start of baseline measurement, with temperature up to 38.2°C. During this she was sedated only with propofol (dose doubled from baseline measurement, morphine discontinued), without neuro-muscular blockade or vaso-active drugs. Measurement lasted 70 minutes, temperature decreased from 38.2 to 37.4°C. No paracetamol had been given prior to calorimetry during this admission.

Case 5:

This 2-year old boy was admitted with croup. Subsequently Group A Streptococcus was cultured from tracheal secretions. He developed fever soon after admission to PICU. Baseline calorimetry measurements were taken on day 1, but he had no fever within the 4-hour window thereafter. Calorimetry continued for 46 minutes in anticipation of fever as his temperature was 37.8°C. He was sedated with morphine and midazolam, with no neuro-muscular blockade or vaso-active drugs. No paracetamol had been given prior to calorimetry during this admission.

Case 6:

This 15-year old boy was initially admitted with traumatic brain injury, discharged from PICU, but readmitted from the ward with pneumonia. He developed a fever on day 1 of admission. The first calorimetry measurement was taken during fever on day 1 as temperature

decreased from 38.7 to 38.4°C. Two further measurements were taken following recalibration post airway suctioning, with a maximum temperature up to 39.1°C. He was sedated with fentanyl and midazolam initially, however the midazolam was changed for dexmedetomidine during the measurement. The patient had no neuro-muscular blockade or vaso-active drugs. Paracetamol had been given an hour before the first measurement, and then 6 hours later when the temperature was 39.1°C.

Case 7:

This 2-year old boy with Trisomy 21 was admitted post resection of subglottic tissue and ariepiglotoplasty. He became febrile in the early hours of day 4 of admission. A baseline measurement was taken over 33 minutes following this, with a temperature of 36.9°C. The patient was sedated with morphine and midazolam, not on vaso-active drugs or under neuro-muscular blockade. A second measurement was attempted after two hours as there was a rise in temperature (to 37.6°C), but I was unable to get stable measurements with an energy expenditure co-variate >10%. This coincided with a drop in the tidal volumes to just over 100mls. Paracetamol had been given 3 hours prior to the first calorimetric measurement.

Case 8:

A 2-year old girl with meningococcal sepsis developed fever on the day of admission, but the family were not approached at the time as she was too unstable. The family were approached on day 2 of admission and they consented for calorimetry. However, I was unable to get stable measurements, with tidal volumes just over 100mls.

Case 9:

A 5-year old child was admitted with meningococcal sepsis. A baseline measurement was taken on the day admission. At the time he was on adrenaline and noradrenaline infusions. He was sedated with morphine and midazolam and not under neuro-muscular blockade. He

did not develop a fever in the subsequent 4-hour period (or during the remainder of his admission). No paracetamol had been given prior to calorimetry during this admission.

Case 10:

An 11-month old boy was admitted post long gap oesophageal atresia repair. He developed fever on day 2 of admission. Calorimetry was attempted after consenting, but he developed a large leak with small tidal volumes (60-70ml) – therefore calorimetry was abandoned.

Case 11:

This 11-year old boy was initially admitted post-spontaneous intra-parenchymal brain bleed. On day 10 of admission he developed a ventilator-associated pneumonia with a new onset fever. Calorimetry was undertaken on day 11 of his admission during a fever, with his temperature decreasing from 38.9 to 37.9°C. However, the EE covariance increased to >10% halfway through the 100 minute measurement, due to water in the ventilator circuit. A further measurement was attempted but also yielded unstable measurements as the patient was disconnected for airway suctioning shortly after. The patient was not sedated, not paralysed and was not on vaso-active drugs. Paracetamol was given in the hour before calorimetry was started.

Case 12:

This 23-month old girl with an undiagnosed immunodeficiency syndrome and previous haemolytic uraemic syndrome was admitted with pneumonia. Although her parents initially consented for calorimetry, this was then withdrawn before a measurement could be taken.

The demographic details and duration of calorimetry measurements are summarised in Table 4.1.

Patient ID	Age (months)	Sex	Weight (kg)	Height (cm)	Duration of calorimetry (minutes)	Temperature range(°C)
1	140	F	58	158	72	38.5-38.8
2	13	M	10	82	12	37.5
3	56	M	18.5	106	63	37.5-37.8
4	191	F	28	137	100	37.4-38.2
5	22	M	14	85	46	37.7-37.8
6	169	M	70	178	357	38.4-39.2
7	31	M	13.9	83	33	36.9
8	32	F	12	99		
9	68	M	20	111	30	36.8-36.9
10	11	M	11			
11	136	M	37	143	100	37.9-38.9
12	23	F	15.3	88		

Table 4.1: Summary of case demographics and measurements in whom calorimetry was performed. No calorimetry measurements were available for cases 8 and 10 due to low tidal volumes/ increase in leak around endotracheal tube. Case 12 withdrew consent for calorimetry prior to first measurement.

4.4.3 Association between temperature and energy expenditure

The small number of cases especially those with calorimetry measurements during generation of fever or defervescence means that strong conclusions cannot be drawn from the data. Nevertheless, the data are explored to understand changes in individual patients.

The energy expenditure measurements for each patient are plotted against temperature for each patient in Figure 4.4. No consistent pattern was evident in the change in energy

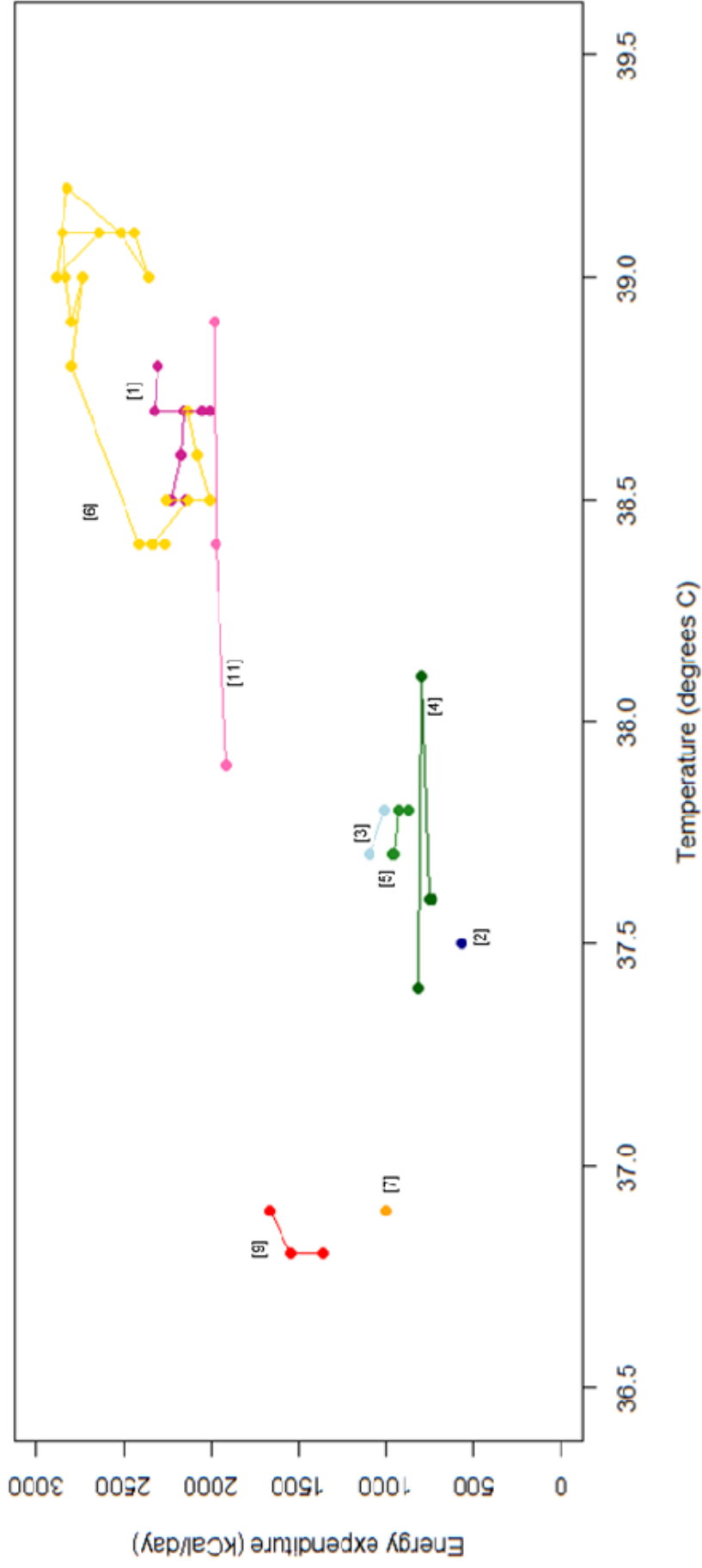


Figure 4.4: Energy expenditure expressed as kCal/day plotted against temperature. Each patient is denoted in a different colour, annotated by patient number. Each dot represents the mean of the measurements over a 10-minute period (or 5-minute period for first reading). There is no consistent relationship between energy expenditure and temperature in each patient (except patients 6 and 11).

expenditure according to temperature. However, energy expenditure increased in case 6 and 11, both of whom had calorimetry measurements over a wide range of temperatures in the febrile range compared to the other cases. Energy expenditure expressed as a percentage of predicted energy expenditure is plotted against temperature in Figure 4.5.

The change in energy expenditure from the minimum temperature to maximum temperature during the rise and fall in temperature is shown in Table 4.2.

During temperature rise, there was an increase in energy expenditure in all 3 patients who had measurements during this phase. The increase in energy expenditure ranged from 12.7-26.1% per °C rise in temperature (although 2/3 children were febrile at the start of measurement).

During the fall in temperature, the change in temperature was much more variable, with energy expenditure increasing on 4/6 occasions. However, the falls in temperature during calorimetry measurements were often small (0.1°C in cases 5 and 9), and not always from a febrile to a non-febrile range. In cases 4 and 11 where calorimetry measurements were available during fever defervescence, there was a modest increase in energy expenditure in case 4 by 1.9% per °C, and a decrease of 3.4% per °C in case 11. No paracetamol had been given to case 4, while case 11 received paracetamol in the hour before calorimetry was started. It is possible that this may explain the differences in energy expenditure.

Multi-variable analysis was performed using multi-level linear regression analysis to determine the change in energy expenditure per °C change in temperature, accounting for changes in heart rate, blood pressure, sedation and vasoactive medication. As none of the patients had neuro-muscular blockade, this was omitted as a variable in the regression analysis. Although sedation status was to be measured by COMFORT score, this was poorly recorded as part of routine care. Therefore, change in sedation dose was also used as an ordinal variable (-1 for a decrease in sedation, +1 for an increase in sedation given, 0 for no change in sedation dose). In addition to using patient identifier as a fixed effect variable as

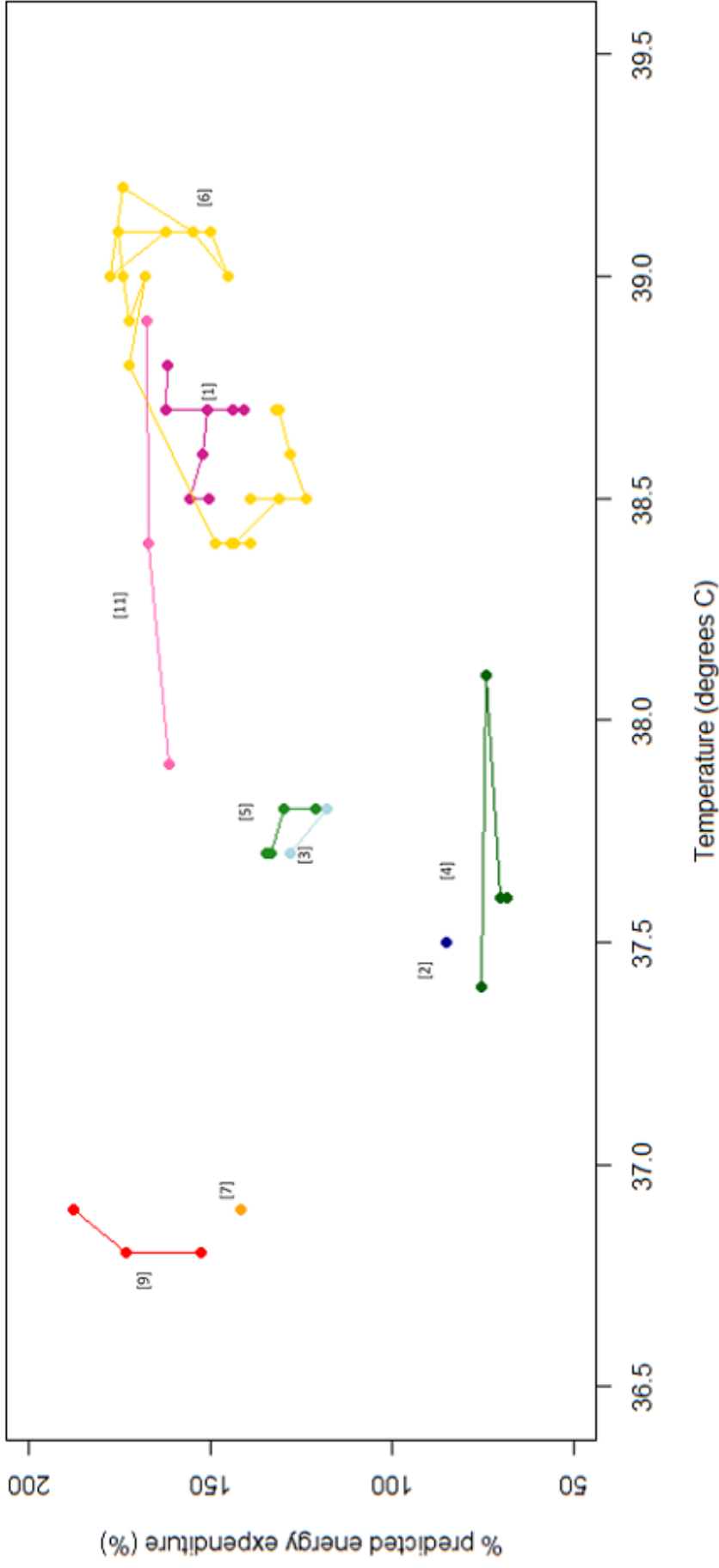


Figure 4.5: Energy expenditure expressed as the percentage of predicted energy expenditure, calculated using the Schofield equation, plotted against temperature. Excluding patients 7 and 9, there is a linear increase in percentage of predicted energy expenditure with temperature ($R^2 = 0.55$)

Case number	Lowest temperature during temperature rise (°C)	Maximum temperature (°C)	Lowest temperature during temperature fall (°C)	Change in energy expenditure (kCal/day)	Change in energy expenditure per °C change in temperature (kCal/day)	Percentage change in energy expenditure per °C change in temperature
1	38.5	38.8		121.9	406.2	17.5
3		37.8	37.7	85.6	856	85.1
4	37.6	38.1		51.0	101.9	12.7
4		38.1	37.4	10.6	15.1	1.9
5		37.8	37.7	61.9	619.3	68.9
6	38.4	39.2		489.1	611.4	26.2
6		39.2	39.0	60.5	302.6	10.7
9		36.9	36.8	-219.3	-2193.4	-131.5
11		38.9	37.9	-68.1	-68.1	-3.4

Table 4.2: The change in energy expenditure during a rise in temperature (red) or a fall in temperature (black). Data shown from 7 patients with 9 calorimetry measurements (case 4 and 6 have two measurements listed each). Three cases had calorimetry measurements during temperature rise. The change in energy expenditure is calculated from by subtracting the energy expenditure during the lowest recorded temperature (or the baseline measurement as in case 4), from the energy expenditure during the maximum temperature. If there was more than one measurement at the same temperature, a mean of these was used. The change is expressed per °C rise in temperature, and as a percentage change from the energy expenditure at the lowest temperature. Six cases had calorimetry measurements during a fall in temperature. The change in energy expenditure per °C is expressed as a percentage of the energy expenditure at the highest temperature – therefore a positive change represents an increase in energy expenditure despite a fall in temperature.

planned a priori, each separate calibration was also added as a fixed effect variable to account for any drift in accuracy of calorimetry measurements. There was no significant co-

linearity detected between variables (even though heart rate and temperature are known to be positively associated as demonstrated in the previous chapter).

A change in temperature was not independently associated with a change in energy expenditure. The only variable that did have a positive association was diastolic blood pressure – energy expenditure increased as diastolic blood pressure increased (Table 4.3). However, the small number of data points available makes this analysis difficult to interpret.

Variable	Multi-level linear regression coefficient	95% confidence interval for regression coefficients
Temperature	154.9	-7.7, 472.3
Heart rate	7.4	-5.6., 13.8
Systolic blood pressure	3.3	-2.6, 10.5
Diastolic blood pressure	9.8	2.8, 19.5
Vasoactive Inotrope Score	21.6	-7.0, 51.5
Increase in sedation	-46.4	-3.1, 219.8

Table 4.3: Linear regression coefficients following multi-level linear regression analysis of energy expenditure, with 95% confidence intervals. Only diastolic blood pressure was independently associated with change in energy expenditure – an increase in diastolic blood pressure by 1 mmHg was associated with an increase in energy expenditure by 9.8 kCal/day (95% CI 2.8-19.5 kCal/day).

4.4.4 Association between temperature and VO₂, VCO₂, RQ

As with the energy expenditure analysis, these results must be interpreted with caution given the small sample size. The change in oxygen consumption from the minimum temperature to maximum temperature during the rise and fall in temperature is shown in Table 4.4. There was no consistent association between oxygen consumption and temperature in each

patient (Figure 4.6). Although an absolute increase in oxygen consumption with temperature across patients is apparent from Figure 4.6, when indexed for weight there was no relationship between oxygen consumption and temperature (Figure 4.7). Following multi-level linear regression as described above for energy expenditure, temperature was not independently associated with oxygen consumption (regression coefficient for temperature 32.7, 95% CI -7.5, 77.0).

Case number	Lowest temperature during temperature rise (°C)	Maximum temperature (°C)	Lowest temperature during temperature fall (°C)	Change in oxygen consumption (ml/kg/min)	Change in oxygen consumption per °C change in temperature (ml/kg/min)	Percentage change in oxygen consumption per °C change in temperature
1	38.5	38.8		16.5	54.9	16.8
3		37.8	37.7	7.3	73	51.7
4	37.6	38.1		6.4	13.9	13.1
4		38.1	37.4	3	4.3	3.8
5		37.8	37.7	8.5	85.0	66.5
6	38.4	39.2		89.4	111.7	34.3
6		39.2	39.0	11.7	58.6	14.1
9		36.9	36.8	-34.3	-343.2	-1.4
11		38.9	37.9	-1.3	-1.3	-0.5

Table 4.4: The change in oxygen consumption during a rise in temperature (red) or a fall in temperature (black). As in Table 4.2, for the three cases that had calorimetry measurements during a rise in temperature, the increase in oxygen consumption ranged between 13-34% above baseline per °C increase in temperature.

Similarly, there was no association between carbon dioxide production and temperature (Figure 4.8). There was no rise in carbon dioxide production with temperature in case 6. Once again, any suggestion of an increase in absolute carbon dioxide production with

temperature is no longer apparent when carbon dioxide production is indexed for weight (Figure 4.9). Temperature was not independently associated with carbon dioxide production (regression coefficient for temperature -11.2, 95% CI -45.8,30.8).

As expected from the above results, there was no consistent relationship between the respiratory quotient and temperature (Figure 4.10). This was borne out following multi-variable analysis (regression coefficient for temperature -0.04, 95% CI -0.14,0.08)

None of the patients who had calorimetry measurements had simultaneous cardiac output monitoring and only one patient had an arterial catheter in situ. Therefore, the oxygen extraction ratio could not be calculated.

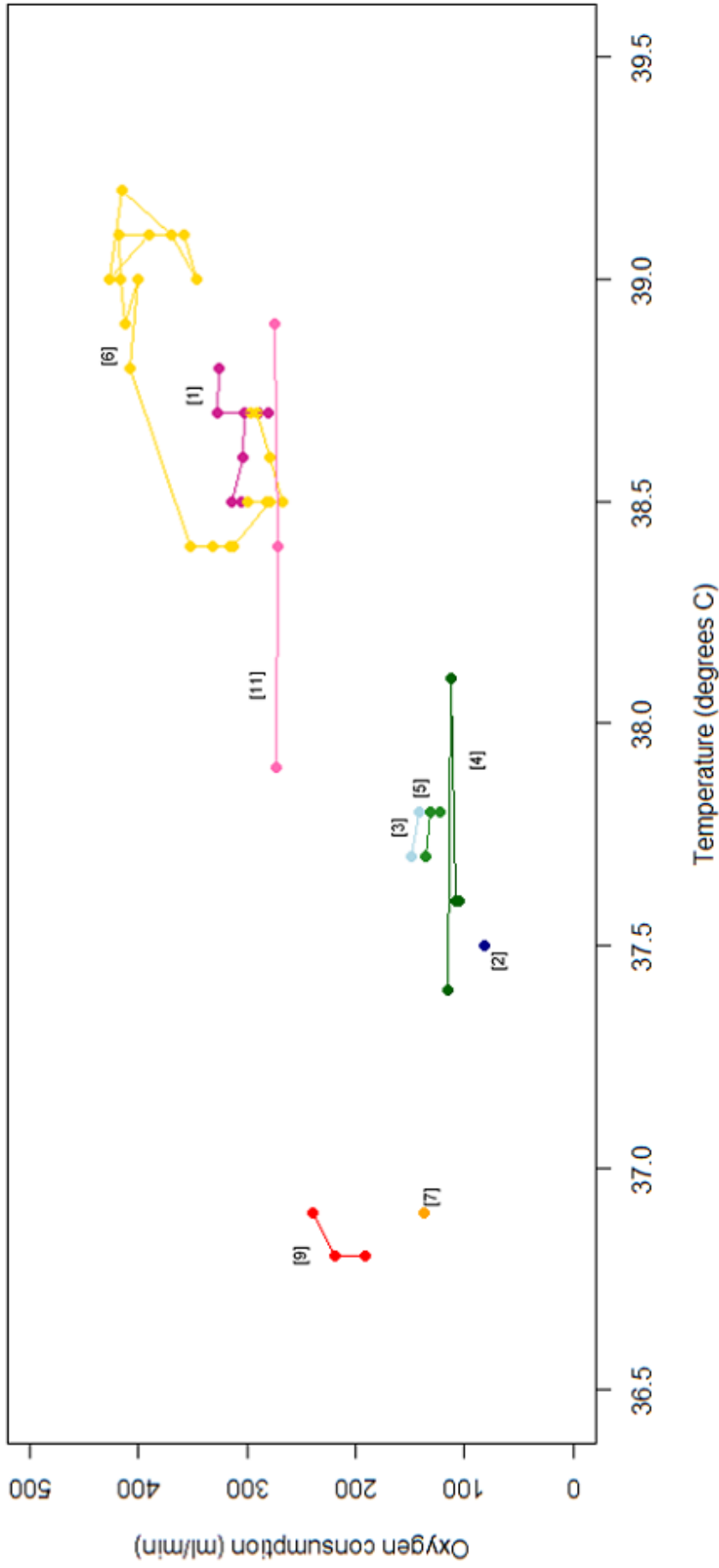


Figure 4.6: Oxygen consumption expressed as ml/min plotted against temperature. Each patient is denoted in a different colour, annotated by patient number. Each dot represents the mean of the measurements over a 10-minute period (or 5-minute period for first reading). There is no consistent relationship between oxygen consumption and temperature in each individual patient, apart from an increase in oxygen consumption with temperature in case 6.

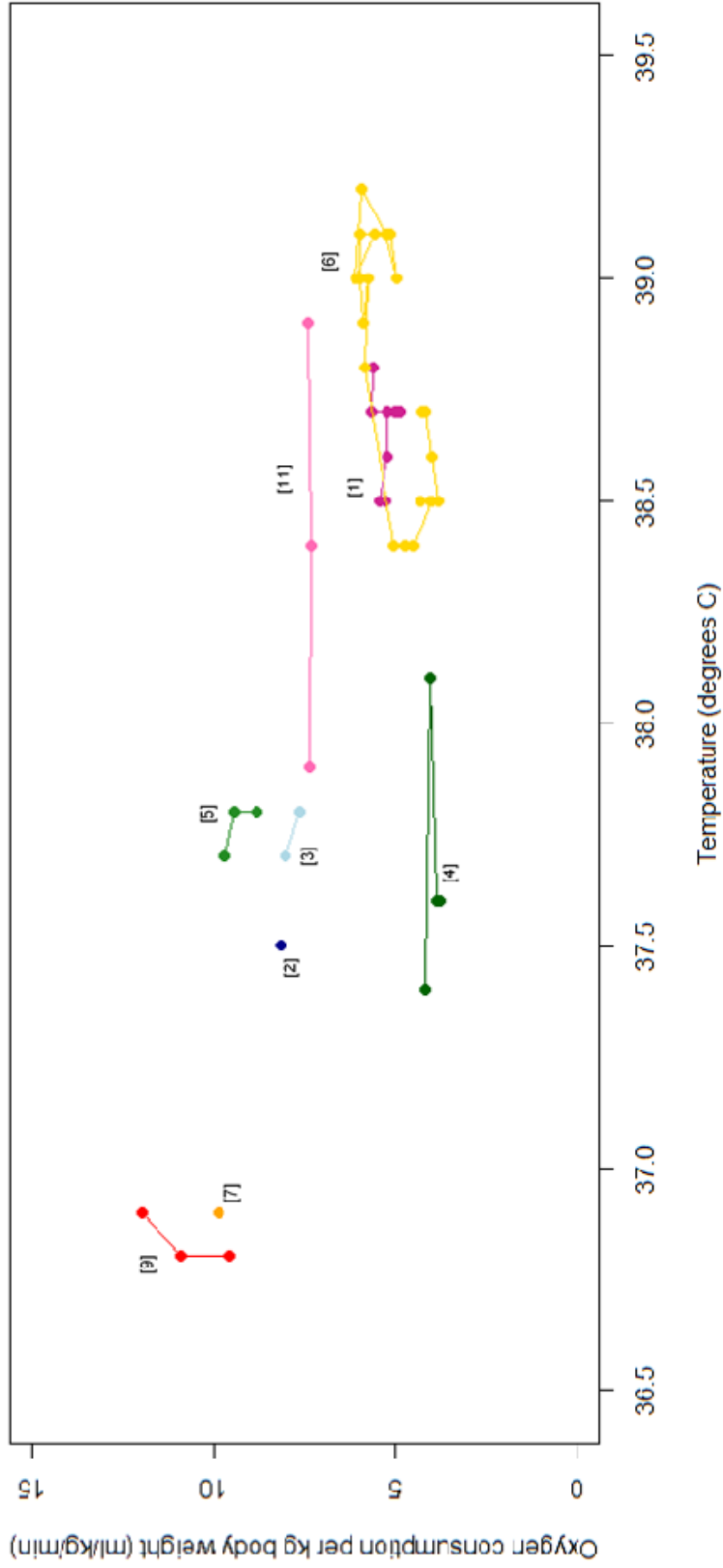


Figure 4.7: Oxygen consumption indexed for weight (ml/kg/min) plotted against temperature. There is no consistent relationship between oxygen consumption and temperature between patients.

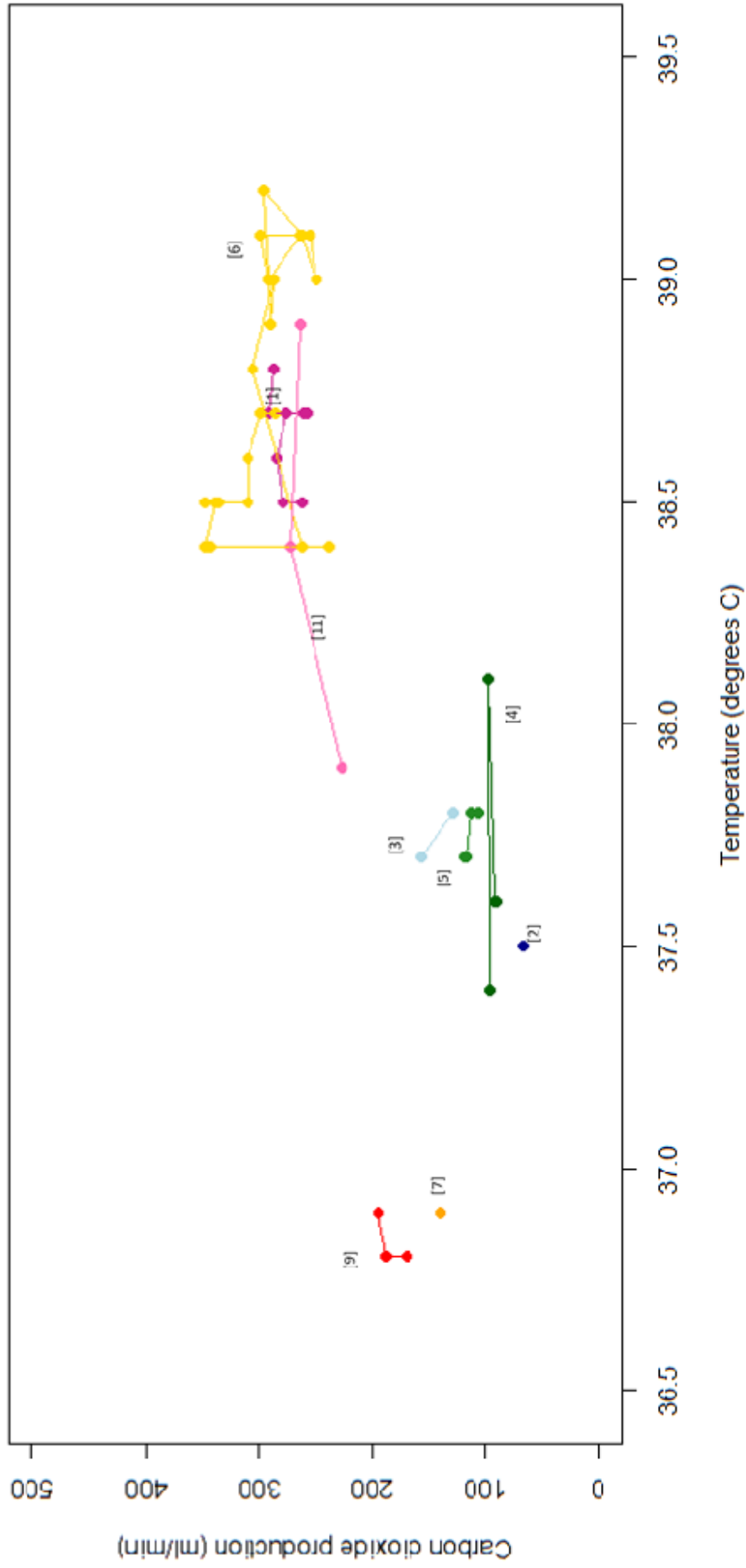


Figure 4.8: Carbon dioxide production expressed as ml/min plotted against temperature. Each patient is denoted in a different colour, annotated by patient number. Each dot represents the mean of the measurements over a 10-minute period (or 5-minute period for first reading). There is no consistent relationship between carbon dioxide production and temperature in each patient.

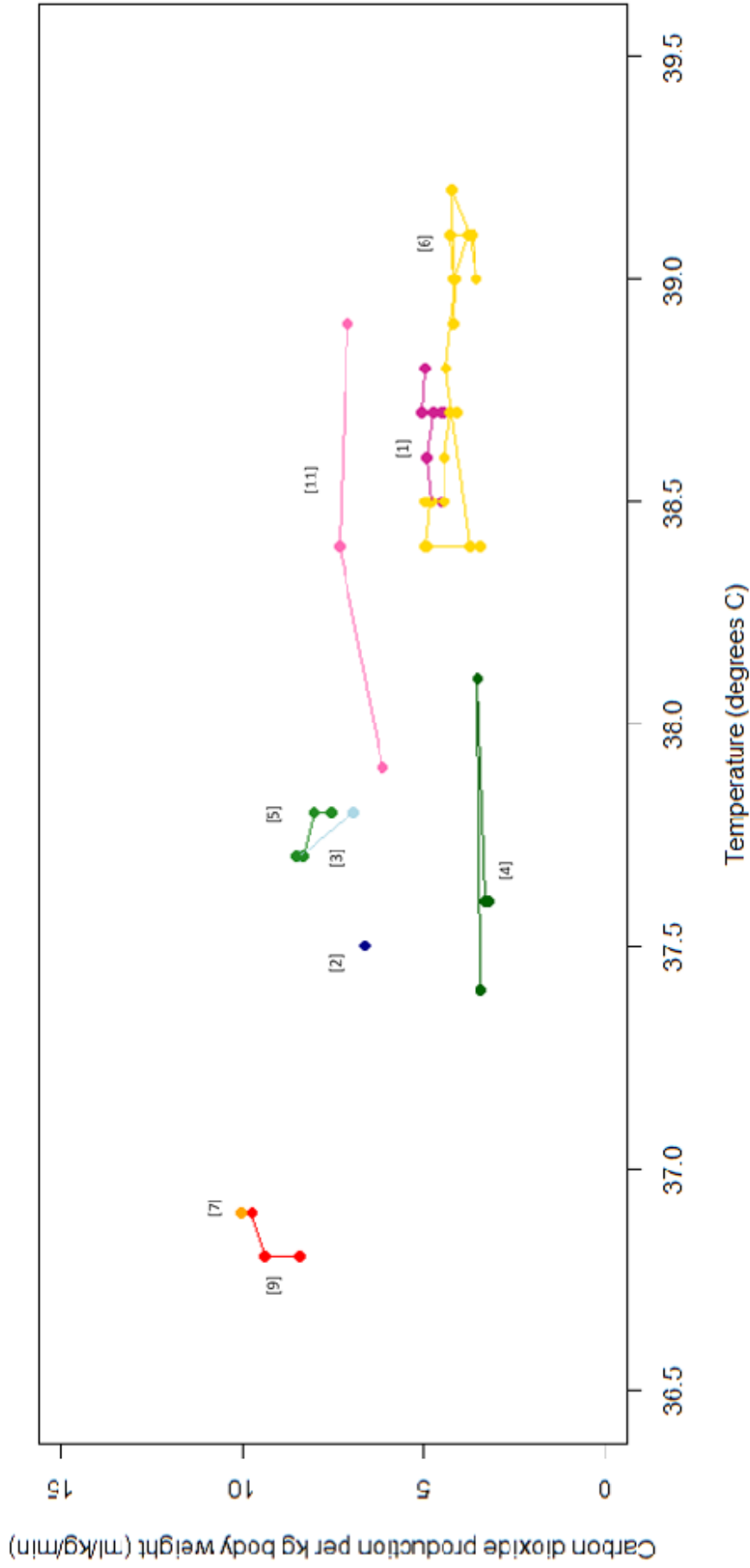


Figure 4.9: Carbon dioxide production indexed for weight (ml/kg/min) plotted against temperature. There is no consistent relationship between carbon dioxide production and temperature between patients.

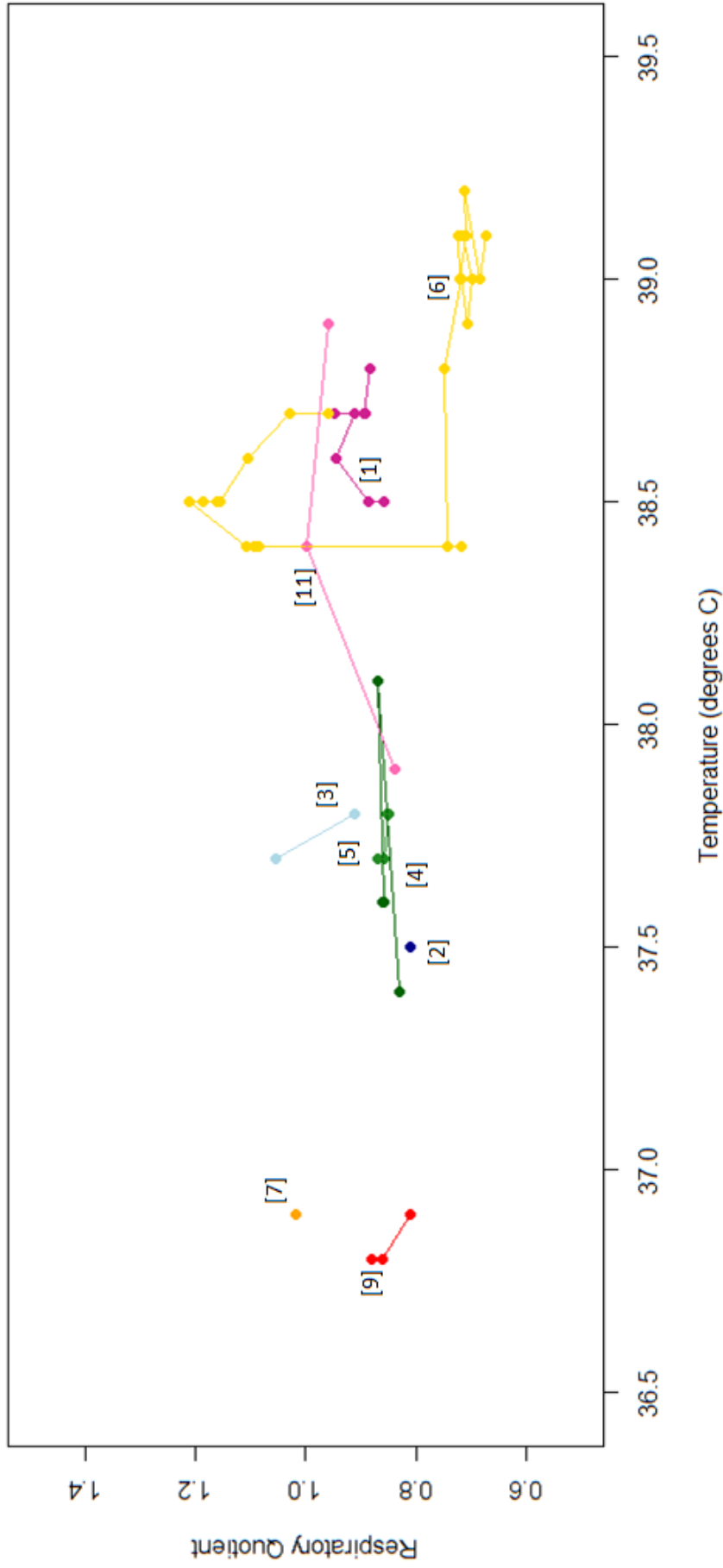


Figure 4.10: Respiratory quotient plotted against temperature. Each patient is denoted in a different colour, annotated by patient number. Each dot represents the mean of the measurements over a 10-minute period (or 5-minute period for first reading). There is no consistent relationship between respiratory and temperature in each patient.

4.5 Discussion

As mentioned above, the small dataset and lack of calorimetry data during generation of fever or defervescence makes these data difficult to interpret. The data were analysed as planned a priori. The results are summarised, and interpreted with caution below, followed by the limitations of the study.

4.5.1 Summary of results

The following observations can be made from the limited data:

- 1) Energy expenditure increased in the three cases where data were available when the temperature was rising. Even though only one of these cases was afebrile at the start, the increase in energy expenditure is between 12.7-26.2% per °C rise in temperature. This is consistent with historical reports of increased energy expenditure with temperature during fever. For oxygen consumption, this equated to a 13.1-34.3% rise per °C rise in temperature.
- 2) There is a less consistent pattern with energy expenditure when temperature decreased. Energy expenditure both increased and decreased during a fall in temperature. This is likely due to only small decreases in temperature observed during calorimetry.
- 3) The lack of data did not allow for the detection of any consistent effect of paracetamol in reducing energy expenditure
- 4) When considered in a multi-variable regression model, there was no association between energy expenditure and temperature.
- 5) Similarly, there was no consistent association between oxygen consumption, carbon dioxide production or the respiratory quotient and temperature following multi-variate analysis.

4.5.2 Hypothesis testing and Implications of results in critically ill children

The results of this study do not provide any conclusive evidence regarding the change in energy expenditure with fever. This is largely due to the small sample size and lack of data from children before, during and after fever, as planned a priori.

During critical illness, multiple physiological processes, measured and unmeasured, could influence energy expenditure. For example, ongoing inflammation, healing and repair, effects of ventilation and drugs can all potentially change metabolic rates, and therefore, energy expenditure. Multi-variable analysis would account for these other confounders. In the analysis of the effect of temperature on energy expenditure in fever, heart rate, blood pressure, effects of sedation and vasoactive drugs were used to account for potential confounders. These were chosen to reflect changing states such as ongoing shock, changes in sedation and awareness or stimulation following physiotherapy or similar ICU interventions. Following linear regression analysis, energy expenditure did not change with temperature.

This study was designed to identify changes in energy expenditure during the rise and fall in temperature with fever, similar to the earlier studies by Barr, Cecil and DuBois in adults. The observation of an increase in energy expenditure during the rise phase of temperature in fever in cases 1, 4 and 6 is consistent with the observations of Barr et al. However, this increase in energy expenditure with temperature was not seen in all cases. This would be consistent with the study by McIntyre and Hull, who also demonstrated the effects of fever on energy expenditure were variable.

It is difficult to explain an increase in temperature without energy consumption. The likeliest possibility is around the timing of measurement of energy expenditure. As Barr, Cecil and DuBois described, energy expenditure increases early in the generation of fever, thereafter temperature is maintained through a balance of increases energy expenditure and reduction

in heat loss. It is possible the study as designed did not capture the rise in energy expenditure in some of these children.

Diastolic blood pressure was independently associated with energy expenditure in the multi-variable model using the limited data (Table 4.3). It is possible that diastolic blood pressure was as a surrogate marker of vasoconstriction in these children: once already vasoconstricted, greater energy would be required for thermoregulation. Given the sample size, however, this is speculative. When the model was re-run using temperature and diastolic blood pressure as an interaction term post-hoc, none of the variables were significantly associated with energy expenditure (results not shown).

During the fall in temperature, the effect on energy expenditure was more variable. As described by Barr et al, during fever defervescence, heat elimination exceeded heat production; eventually heat production falls to restore normal body temperature. The above observations could be explained by the same effect: in some children heat production continued but was exceeded by heat elimination. Energy expenditure continued to rise, but if calorimetry continued, this may have eventually decreased. The decrease in temperature observed during calorimetry were small: changes of 0.1°C could be within the margins of error of the clinical thermometers [US Food and Drug Administration 2016]. The increase in energy expenditure seen with these small decreases in temperature may reflect the energy required to defend the febrile temperature against surface heat loss. In the two cases where the fall in temperature exceeded 0.5°C , the change in energy expenditure was modest, with a 3.4% decrease in energy expenditure per $^{\circ}\text{C}$ in one, and a 1.9% increase per $^{\circ}\text{C}$ in the other. This may reflect true defervescence.

Cases 6 and 11 in particular show an increase and decrease in energy expenditure with a rise and fall temperature respectively. This is most likely because the calorimetry was undertaken during a significant rise in temperature in the fever range for case 6 and a fall in temperature from fever range in case 11. It is interesting that both cases were children with previous brain injury, who were febrile with subsequent pneumonia. It is possible that brain

injury in both decreases thermoregulatory capacity by preventing heat loss. Therefore, thermogenesis, and consequently energy expenditure, may have been required to increase temperature in both.

The effect of temperature on oxygen consumption and carbon dioxide is similar to that on energy expenditure (unsurprising, given that energy expenditure is calculated from both values). The respiratory quotient was mostly between 0.8 and 1.0, with no change with temperature. Case 6 is an exception: the respiratory quotient fell to below 0.7 as the temperature increased to 39°C. It is possible to speculate that to generate greater temperatures, the patient switched from glycolysis to lipolysis.

4.5.3 Limitations

This study has several limitations – as a result no conclusive evidence can be drawn from it.

- 1) Study design: The study was designed to observe the changes in energy expenditure with a rise and fall in temperature during fever and defervescence. This was intended to replicate the work of Barr and colleagues – this has never previously been described in either critically ill patients, or children. The plan included identifying children who are at risk of developing a fever, obtaining a baseline measurement while they were afebrile, and then when they became febrile, till they defervesced, either through anti-pyretic intervention or without.

Identifying children likely to develop fever was difficult. As evident from the epidemiology work in Chapter 2, most children with suspected infection are febrile early in their admission. As emergency admissions largely occurred out of normal working hours, and fever often occurred within the first 6 hours of admission, many children with fever were missed.

The likelihood of fever decreases over the first four days of admission. This may be due to anti-pyretic interventions – this study did not seek to prohibit this as it was a

non-interventional study. Part of this study was coincident with the FEVER pilot trial, which compared a permissive (treating fever at a temperature threshold of 39.5°C) versus a restrictive (treating fever at a temperature threshold of 37.5°C) treatment strategy for fever [Peters 2019]. Despite this, not many children could be identified where the temperature predictably rose within the febrile range. This is consistent with the results of the pilot trial – while there was separation between the two randomised arms, the mean difference in temperature was only 0.5°C.

Most children were recruited once they were febrile (4/7 children with valid calorimetry measurements). In 2 of these children the temperature did not recede within 6 hours of the first measurement – these children represented the small proportion of children with persistent fever on PICU, as described in Chapter 2. It is difficult to know if these children have different thermoregulatory pathways compared to the majority of children, for example, they may be uncoupled. The findings in these children may not be generalisable.

The exclusion criteria limited the number of children who could be approached for recruitment. The exclusion criteria matched those that had been used in the FEVER feasibility study design. In particular, fever was common in children who were admitted with brain injury as a primary diagnosis or status epilepticus. The reason for excluding these children was because fever may need to be treated aggressively to prevent further seizures, and thermoregulation may be impaired. The observation that the two children that showed an increase in energy expenditure with a fever both had previously suffered brain injury, strengthens this suspicion.

- 2) Restrictions of indirect calorimetry: Indirect calorimetry introduces several restrictions. Most importantly, the MGC Diagnostics Ultima CCM calorimeter (and all other calorimeters marketed at the time of writing) are only licensed for use in patients with greater than 100ml tidal volumes. This is due to the sampling rate of a breath by breath analyser. The MGC Diagnostics Ultima CCM samples inspired and

expired gas at a constant rate of 125ml/min. For children with small tidal volumes this may affect ventilation. Typically, patients on PICU are ventilated at tidal volumes of 4-7ml/kg – therefore the smallest children that the MGC Diagnostics Ultima CCM calorimeter could be used on would be 13kg. Based on the experience of colleagues, calorimetry was proposed to be undertaken in children as small as 10kg. Although case 2 was the smallest child recruited weighing 10kg, he generated tidal volumes >100ml even on minimal ventilator settings. Calorimetry measurements could not be obtained in case 8 and 10 who had tidal volumes less than 100ml, and in case 7 when the tidal volumes dropped below 100ml. In addition, a leak around the endotracheal tube >5% of the tidal volume is not tolerated in estimating energy expenditure – this is not uncommon in PICU given the use of uncuffed endotracheal tubes in younger children. As a result, no conclusions can be drawn about energy expenditure in very young children with fever. It is hypothesised in these children that elimination of heat loss may be a major mechanism of generating febrile grade temperatures.

The sensitivity of the calorimeter decreases if the fraction of inspired oxygen is >0.60. This is more likely early during PICU admission, and some children could not be recruited despite being at risk of developing a fever, or being febrile, because of this. Also, children ventilated with a high frequency oscillator could not be recruited – once again this is often early during a PICU admission, when fever is more likely.

The accuracy of the MGC Diagnostics Ultima CCM is poor compared to the extensively used Deltatrac II and Douglas Bag [Black 2015]. However, the Deltatrac II is no longer manufactured nor supported, and the Douglas Bag technique is technically difficult, with large potential for error. The MGC Diagnostics Ultima CCM has been used in published paediatric studies on PICU [Mtaweh 2014], and therefore was thought to be the best technique available at the time of conducting the study.

Finally, the calorimeter is not routinely used in PICU given the problems stated above. Some parents were not willing to provide consent for its use, as they felt their

children were too vulnerable to suffer harm from a piece of equipment not routinely used in young children.

- 3) Time course of changes in variables and effects on energy expenditure: Data were analysed under the assumption that energy expenditure would change along with measured temperature. Barr and colleagues' work however suggests that this may not necessarily be so. They were able to define distinct stages in fever including prodromal stages prior to temperature rise. Energy expenditure may increase before temperature rises, which may not have been detected in the analysis, particularly if calorimetry only started once the child was febrile. Similarly, the decrease in energy expenditure may precede defervescence.

Energy expenditure changes associated with sedation and vaso-active drug dose changes, as used in the multi-variable analysis may also occur over longer or shorter time periods.

- 4) Lack of cardiac output monitoring: It had been initially planned to also study oxygen extraction, using oxygen delivery estimates from cardiac output monitoring. However, none of the children had cardiac output monitoring in situ at the time of calorimetry. Most children did not have arterial lines. In these children suprasternal Doppler could have been used. In those with arterial lines, pulse contour analysis could have been used as described in Chapter 3. However, calorimetry was an involved process which required careful monitoring, particularly given the unfamiliarity of the MGC Diagnostics Ultima CCM within the intensive care unit. Set up of the calorimeter took time: during times when temperature was rising or falling, this was prioritised to measure changes in energy expenditure. Therefore, additional cardiac output monitoring was not carried out.

4.6 Conclusions

The objective of this chapter was to quantify the increase in energy expenditure required to generate a fever in critically ill children. While critically ill adults had been reported to have a 10-13% increase in energy expenditure per °C rise in temperature, this had mainly been derived from cooling experiments. In children thermoregulation through the control of heat elimination could be more important. The measurement of energy expenditure during, before and after fever proved difficult, due to a combination of the limitations of indirect calorimetry and the difficulty in predicting who would develop a fever while invasively ventilated on PICU. Most children were recruited when febrile or did not develop a fever post-baseline measurement. Although the small sample size meant that the hypothesis could not be adequately tested, in the three children who had a rise in temperature during calorimetry, the increase in energy expenditure ranged from 12-26% per °C rise in temperature. This is consistent with previous reports in adults. The change in energy expenditure was lot less predictable during a fall in temperature. This is consistent with previous reports demonstrating that heat elimination rather than decrease in production reduces body temperature.

While fever may increase energy expenditure and therefore oxygen consumption, this may only be of consequence in critical illness if this additional demand for oxygen cannot be met, or the additional demand for energy cannot be afforded (or occurs at the expense of more important processes). Although intended, concomitant measurement of oxygen consumption and delivery was not achieved in the same patients. In the following chapter, I will explore the effects on temperature, and in particular, fever on the changes in oxygen delivery in critically ill children. In addition, I will also describe the effects of the paracetamol oxygen delivery, as the most used anti-pyretic intervention.

Chapter 5: Haemodynamic effects of fever and its treatment

5.1 Introduction

If fever is associated with an increase in oxygen consumption, if this is not matched by an increase in oxygen delivery, an oxygen debt will occur. The findings in the previous chapter, although limited by the small numbers, were consistent with adult data suggesting an increase in oxygen consumption in the region of 10-13% per °C rise in body temperature [Manthous 1995; Hata 2008; Bruder 1998; Gozzoli 2004]. In this chapter, I explore the effect of temperature and fever on oxygen delivery, in particular haemodynamic changes.

The haemodynamic effects of body temperature and fever in particular have long been recognised [Altschule 1945b]. Heart rate increases with fever. An increased heart rate is often used as a marker for circulatory inadequacy i.e. shock. Treatment is directed to restore the heart rate back towards 'normal' – for example, with the use of fluids or inotropic drugs in sepsis. This is particularly so in critically ill children. Fever confounds this.

An increase in heart rate reduces the time the heart spends in diastole. This is the period in the cardiac cycle when the ventricles fill, and the coronary arteries perfuse the myocardium. Reducing diastolic time can lead to both poor filling and impaired myocardial perfusion. Stroke volume can decrease as a result. As cardiac output is a product of heart rate and stroke volume, beyond a certain point, and increase in heart rate can decrease cardiac output.

Peripheral (skin) vasoconstriction is a thermoregulatory mechanism to conserve heat [Morrison 2019]. This may be an important mechanism in raising body temperature during fever, as suggested by Barr et al [Barr 1918] and Boyle [Boyle 2010]. Systemic vascular

resistance could increase following skin vasoconstriction, depending on the relative contribution of the peripheral vascular resistance to the total. Children have a higher surface area to weight ratio compared to adults: the contribution of the skin circulation to the systemic resistance is theoretically greater. This increase in systemic vascular resistance could increase afterload, leading to a decrease in stroke volume. As blood pressure is a product of systemic vascular resistance and cardiac output, blood pressure would be could increase, decrease or remain constant depending on the relative changes in systemic vascular resistance and cardiac output.

Critically ill children are likely to have haemodynamic compromise: myocardial function is often reduced; preload can be reduced due to hypovolaemia, afterload can be too high due to vasoconstriction. ICU interventions also affect these variables: positive pressure ventilation reduces preload and afterload, vaso-active drugs have dose dependent effects on afterload and contractility, extra-corporeal circuits can have variable effects. If fever further adds to haemodynamic compromise, then treatment is desirable.

Treatment of fever can have its own consequences. Paracetamol is the most commonly used treatment for fever in children as shown in Chapter 2. In adults and children, paracetamol has been observed to decrease blood pressure [Schell-Chaple 017; Achuff 2019]. External cooling can cause vasoconstriction: studies of external cooling have reported a decrease in the need for vasoconstrictors [Schortgen 2012].

In this chapter, I explore the haemodynamic consequences of fever in critically ill children admitted to PICU, and of paracetamol, the most commonly used treatment for fever. I use high-resolution patient bedside monitor data to evaluate the relationship between the vital signs: continuously measured temperature, heart rate and blood pressure. I focus on these relationships in the fever range ($>38^{\circ}\text{C}$). I use pulse contour analysis of the arterial pressure waveform to examine the effects of the rise in temperature during fever on more complex haemodynamic variables. Finally, I evaluate the change in blood pressure following a

paracetamol dose in critically ill children, with the haemodynamic mechanisms that underpin this.

5.2 Aims and hypothesis

Aims of the study:

- (i) To describe the effect of temperature on heart rate and blood pressure in children admitted to ICU using high-resolution vital sign data
- (ii) To describe the effect of fever on heart rate, stroke volume, cardiac output, vascular resistance and blood pressure
- (iii) To describe the effect of paracetamol on haemodynamic variables in children on PICU with and without fever.

Null hypotheses:

Heart rate changes in critically ill children with fever are not different from those described in non-critically ill children

Cardiac output either does not change, or decreases with fever

Fever does not increase systemic vascular resistance

Paracetamol is not associated with a change in blood pressure in critically ill children

Alternative hypotheses:

In critically ill children, heart rate rises by less than 9-10 beats/ $^{\circ}$ C increase in temperature

Cardiac output increases with fever

Systemic vascular resistance increases following fever

Paracetamol is associated with a decrease in blood pressure in critically ill children

5.3 Methods

5.3.1 Effect of temperature on heart rate and blood pressure in PICU using continuous temperature data

Study design and setting: This was a retrospective observational study using high frequency data recorded every 5 seconds from patient monitors for children admitted to PICU/NIC at Great Ormond Street Hospital.

Population: Data from all children admitted to the PICU/NICU at Great Ormond Street Hospital between 1st January 2016 and 31st December 2016 and who had continuous central temperature monitoring were studied. Children from the cardiac ICU were excluded from this analysis because heart rate can be manipulated using electrical pacing in children post cardiac bypass. Children were identified initially by searching the electronic health record (Philips ICCA, Philips, The Netherlands) using an SQL query using hospital numbers of all children admitted to PICU/NICU in 2016 and the presence of a temperature recorded as being 'oesophageal', 'rectal', 'bladder' or 'core' [Appendix]. These were the central temperature recording modalities identified during the epidemiological studies outlined in Chapter 2.

Data sources and variables: Vital sign data for children with central temperature monitoring were downloaded from the Etimetry T3 recording system, which records and stores bedside monitor data at 5 second frequency. Data on central temperatures, heart rate, systolic, diastolic and mean blood pressures, and the time of the recording were extracted from the system. Temperatures less than 32°C were discarded as spurious, as they are usually seen if the probe is no longer in the oesophagus, or sometimes when nasogastric feed is given, and the nasogastric tube is in contact with the oesophageal probe. Heart rates >220 beat/min were excluded as spurious, although no heart rates below a lower limit were

excluded. Systolic blood pressures <30 mmHg and >250 mmHg were excluded as spurious, as were diastolic blood pressures <10 mmHg and >200 mmHg, and mean blood pressures <16 mmHg and >216mmHg.

The age and sex of the child were identified from the admission data as submitted to PICANET.

Bias: High frequency data are only available for bedside monitor data. Other interventional data on variables such as sedation, drugs, stimulation and ventilation are recorded in the electronic health record and done so at hourly intervals. These variables could confound both heart rate and temperature. However, no confounders including underlying pathology were considered in this analysis because of mismatch in data capture frequencies and therefore unavailable data. Given the size of the data analysed, it was assumed that a univariable analysis will provide an accurate estimate of the relationship between heart rate and temperature.

Study size: Data were collected for children admitted over a single calendar year. Approximately 25% of admissions were anticipated to have continuous core temperature monitoring i.e. a total of 250 children. Work from other studies on high frequency data had suggested a 30% data loss due to loss of recording and missing labelling of recorded data. Approximately 200 children would therefore have continuous temperature data recorded. Core temperature probes are used early in admission when the child is most likely to have temperature and physiological instability. Assuming core temperature measurements being available for 24 hours, it was anticipated that this would result in approximately 3.5 million data points from 200 patients. This was thought to be sufficient to detect a reasonably precise estimate of the heart rate and temperature association.

Data analysis: The temperature effect on heart rate have been previously described as linear, even though Thompson et al demonstrate a non-linear increase in heart rate with temperature, especially in the younger age group [Thompson 2010]. As a first step, data

were analysed using multi-level linear regression. Heart rate or blood pressure were used as the dependent variable, temperature as the independent variable and unique patient identifier and a continuous recording identifier (in case of multiple admissions, or different periods of core temperature measurement) as the different levels. This allowed for the model to account for the relationship between heart rate and temperature with a variable number of repeated measures per patient per admission. Secondly, as a simple method to detect changes over different temperature ranges, the regression analysis was repeated for 1°C intervals between 36-40°C i.e. all values with corresponding temperature between 36-37°C, 37-38°C, 38-39°C and 39-40°C were analysed separately. The co-efficients for temperature from the models were used to construct a crude non-linear curve to represent the effects of temperature on heart rate across the different temperature ranges.

In addition, heart rate and blood pressure data were standardised to provide z-scores. The reference data used for heart rate were those published by Fleming et al, using data from 143,346 children identified from 69 published studies [Fleming 2011]. The reference data for blood pressure were those from the Fourth Report of the US NIH Task Force on blood pressure in children [National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004], with data for children under 1 year from the Second Report [National Heart, Lung, and Blood Institute 1987]. Only systolic and diastolic blood pressure centiles were reported in the Second Report, therefore mean blood pressure was omitted in this analysis. As height data were not routinely available, I assumed the 50th centile for height. Z-scores were calculated using the LMS method described by Cole et al [Cole 1990]. The use of z-scores allowed for comparison of heart rate and blood pressure data without the need for an even distribution of ages, as is unlikely for a PICU population (over half the half the admissions are for children <2 years). The z-scores were analysed as above using multi-level linear regression.

Patient consent: Individual patient consent was not sought as only routine measured and recorded clinical data were retrospectively analysed, with minimum patient identifiable

information recorded or reported. This was approved by the Great Ormond Street Hospital Research Governance department who waived the need for ethical approval (R&D number 19HL03).

5.3.2 Effect of temperature and fever on advanced haemodynamic variables

While large volume, high-resolution data can inform about interactions between temperature and heart and blood pressure, no information on the mechanism behind them can be gleaned from it. Also, while the size of the high-resolution data can improve the signal-to-noise ratio (e.g. noise from confounders within PICU care such as use of vaso-active drugs, stimulation from medical procedures and physiotherapy etc.), smaller data sets with confounder information are needed to validate this.

Study design and setting: This was a prospectively analysis of routinely collected patient data using stroke volume estimations from pulse contour analysis for patients admitted to PICU/NICU.

Population: Data were collected from children who underwent continuous cardiac output monitoring for a period of their admission, over a 12-month period (October 2014-15) on the PICU/NICU at Great Ormond Street Hospital. The decision to monitor cardiac output was made by the treating clinical team to aid clinical decision making. All children had to have indwelling arterial catheters to analyse the pulse waveform. Children from the cardiac ICU were not included as pulse contour analysis was not used for cardiac output monitoring.

Data sources and measurement: The LiDCOrapid pulse contour analyser (LiDCO Ltd, UK) was used to estimate stroke volume (Figure 5.1). Pulse contour analysis uses the arterial pulse waveform as transduced from the arterial catheter, to estimate the stroke volume using a proprietary algorithm. Cardiac output is derived from stroke volume and heart rate (cardiac output = stroke volume x heart rate). Systemic vascular resistance is calculated from the



Figure 5.1: The LiDCOrapid Pulse Contour Analyser. The pulse contour analyser is plugged into the monitor module which received input from the arterial transducer. Data that generates the arterial waveform are analysed by the pulse contour analyser to provide estimates of haemodynamic variables. The blood pressure (systolic, mean and diastolic), heart rate (HR), cardiac index (CI) and systemic vascular resistance index (SVRI) measurements are displayed in real time.

mean arterial pressure (MBP), central venous pressure (CVP) and cardiac output (systemic vascular resistance in $\text{dynes}\cdot\text{cm}^{-5}\cdot\text{sec} = (\text{MBP} - \text{CVP}) \times 79.9/\text{cardiac output}$ [Tibby 2003].

While mean arterial pressure is continuously sampled by the LiDCOrapid analyser, central venous pressure is treated as a static variable – although this defaults to 7 cm H₂O, it can be altered according to measurements of CVP at any time. Values are indexed according to body surface area estimated from weight and height. The LiDCOrapid pulse contour analyser uses a nomogram to estimate aortic capacitance. This was validated using the lithium dilution technique in children [Linton 2000]. However, the LiDCOrapid pulse contour analyser does allow for calibration against an alternative method of cardiac output measurement. Although not undertaken in a standardised fashion, the LiDCOrapid was calibrated using supra-sternal Doppler estimations of the cardiac output using the USCOM 1a cardiac monitor (USCOM Ltd, Aus). However even without calibration, trends in stroke

volume, cardiac index and systemic vascular resistance index were assumed to remain accurate irrespective of absolute values [Thiele 2015].

In addition, pulse contour analysers have been noted to show a drift in calibration, described over a period of 2-4 hours [Boyle 2007]. While the product manufacturers suggest that the LiDCOrapid pulse contour analysis algorithm is more stable than this, this was not systematically tested. Where possible, the LiDCOrapid was recalibrated using suprasternal Doppler periodically to minimise changes in calibration. The continuous data were used regardless of calibration given that comparison was made between time-points within the recording for the same patient. Although many periods of analysis were in the period of 6 hours, longer recordings may have been confounded by calibration drift.

Data collection: Data were downloaded directly from the LiDCOrapid machines onto the Great Ormond Street computer network as .csv files. This included the measured heart rate (HR), mean arterial blood pressure (MBP), cardiac output and index (CI), stroke volume and index (SVI) and systemic vascular resistance index (SVRI). Data points with an unreliable signal (as identified by the monitor - for example when the arterial line was being sampled) were excluded. Data were variably compressed according to the length of recording. Therefore, the frequency of cardiac output monitoring data was not uniform across patients – varying between every 3 seconds to every 8 seconds. Once re-calibrated, data were treated as separate episodes from the same patient; therefore, data pre- and post-calibration were not compared with each other (each episode was referred to as a 'calibration episode').

Temperature data were collected manually from the Electronic Health Record. Temperature was recorded at least every four hours in usual clinical care, although if measured continuously (i.e. using an oesophageal, rectal or bladder thermometer) this was recorded hourly. If data from multiple modes of measurement (central, axillary or skin) were available, the central temperature was used preferentially. In addition, data were collected from the Electronic Health Record regarding confounders. Inotrope and vasoconstrictor data were

collected as doses expressed in microgram/kg/hour (or units/kg/hour for vasopressin): these were collected for adrenaline, noradrenaline, dopamine, dobutamine, milrinone and vasopressin. These drugs were all likely to have an effect on haemodynamic variables. Data were not collected for anti-hypertensives as the use of these were relatively rare, especially for children being monitored using LiDCOrapid. Data were also collected for sedation, furosemide, fluid boluses, mean airway pressure and physiotherapy as categorical variables. Sedation changes were expected to have an indirectly proportional effect on heart rate and blood pressure, secondary to changes in the CI and SVRI. Furosemide and fluid would change volumes status and therefore likely stroke volume and heart rate. Mean airway pressures can change both cardiac preload and afterload, thereby affecting stroke volume. Physiotherapy can be acutely stimulating, and we had observed a change in haemodynamic variables with physiotherapy prior to planning the analysis.

For continuous variable (sedation, mean airway pressure, and furosemide when used as an infusion) 1 indicated an increase from the previous hour, 0 indicated no change and -1 indicated a decrease from the previous hour. For sedation (including opiates, benzodiazepine, $\alpha 2$ agonists, ketamine and chloral hydrate) and furosemide given as bolus doses, 1 indicated a dose given in that hour and 0 indicated none. For fluid, 1 indicated a fluid bolus (>5ml/kg) in that hour, 0 indicated none. This included blood products. For physiotherapy, 1 indicated a physiotherapy event with endotracheal suctioning in that hour, 0 indicated none.

Data for haemodynamic variables were available at a higher frequency (every 3 to 8 seconds between measurements) compared to potential confounder data, typically recorded hourly. Moreover, given the retrospective data collection of confounder data, the exact timing of measurement of the confounder data were not known. Therefore, haemodynamic data were summarised for each hour by using the mean value of 200 measurements around the hour mark i.e. if data were recorded every 3 seconds, mean values between 5 minutes

before (3 seconds x 100 readings) and 5 minutes after the hour were used. Outlier data were removed prior to calculating the mean values.

Bias: Patients were selected by the clinical team: although the study was not publicised, knowledge of the study may have influenced the use of cardiac output monitoring in patients, introducing a selection bias. Information bias was likely to arise from the retrospective data collection of confounder data from the electronic health record, while the haemodynamic data were collected from the LiDCOrapid analyser. This may lead to mismatch in time-stamps: however, as high frequency data from the LiDCOrapid analyser were summarised for the hour, this bias was minimised.

Study size: Data recorded over a 12-month period were analysed. A sample size calculation was not undertaken a priori, although data from a minimum of 20 patients were expected.

Data analysis: Data were grouped according to patient, and each calibration episode per patient. The Spearman correlation coefficient was sought for temperature and a) heart rate (HR), b) stroke volume index (SVI), c) cardiac index (CI), d) systemic vascular resistance index (SVRI), and e) mean arterial pressure (MBP), for each calibration episode per patient. The Spearman correlation coefficient was used as the sample sizes per calibration episode could be as small as 2 pairs of data: the use of the Spearman correlation coefficient increases the robustness of the test, especially if the calibration episode samples are non-normally distributed. The medians of the individual correlation coefficients are reported, to evaluate the correlation between temperature and the haemodynamic variables.

For multi-variable analysis, multi-level linear regression was used. Separate models were used to evaluate the independent effect of temperature on each haemodynamic variable – HR, SVI, CI, SVRI and MBP. Inotrope and vasoconstrictor dose data were skewed towards 0 due to the number of children not requiring vaso-active inotropic drugs. This could not be transformed using common transformations (logarithmic or Box-Cox transformations).

Therefore, inotrope and vasoconstrictor dose data were combined into the Vasoactive Inotrope Score [Gaies 2011] as

$$\text{VIS} = (\text{dopamine dose}) + (\text{dobutamine dose}) + (10 \times \text{milrinone dose}) + (100 \times \text{adrenaline dose}) + (100 \times \text{noradrenaline dose}) + (10000 \times \text{vasopressin dose})$$

The change in VIS was then used as a categorical variable similar to sedation and furosemide data: -1 represented a decrease in VIS, 0 no change in VIS and 1 an increase in VIS.

Given all the other confounders were categorised according to changes within the hour or relative to the previous hour, only consecutive hours with temperature values were used. In order to distinguish these, runs of consecutive hours with temperature data were given a unique sequence identifier.

For example, if temperature data were available for the following hours:

22, 23, 00, 01, 03, 04, 05, 06, 09, 10, 11

then data were divided into the following sequences with runs of consecutive hours:

22, 23, 00, 01 – sequence 1

03, 04, 05, 06 – sequence 2

09, 10, 11 – sequence 3

The haemodynamic variable was the dependent variable; temperature and the confounders were fixed effects variables and a unique patient identifier and unique sequence identifier were random effects variables i.e. temperature and confounders would have a fixed effect on haemodynamic variables, but the magnitude of this effect would vary in different individuals during different measurements (Figure 5.2).

To explore the effect of temperature during the rise to fever grade temperatures, data were selected for continuous stretches of temperature *rise*, with the temperature reaching at least

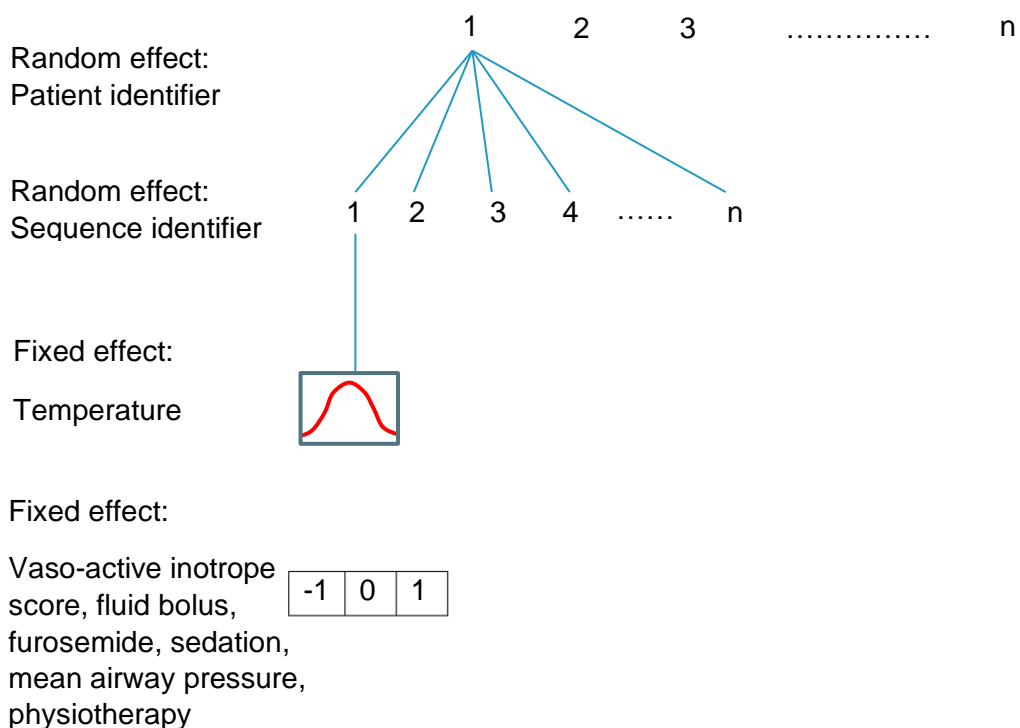


Figure 5.2: Schematic of multi-level model exploring effect of temperature on haemodynamic variables in children admitted to ICU. Haemodynamic variables (heart rate, stroke volume index, cardiac index, systemic vascular resistance index and mean blood pressure) were the dependent variables, temperature was used as a continuous fixed effect variables, other confounders were categorised to an increase, no change or decrease (in the case of fluid boluses and physiotherapy, this was binary); sequence of measurement identifier and patient identifiers were used as random effects variables.

38°C within each continuous stretch. This included continuous sequences above 38°C. If temperatures rose to above 38°C, fell, but then rose again within the febrile range, then the two 'up-slopes' were included separately.

For example, for the following temperature sequence data were divided into the following phases of temperature rise

Hour	22	23	00	01	03	04	05	06	09	10
Temperature (°C)	36.9	37.2	37.4	37.7	38.1	38.3	37.9	38.0	38.1	37.8
Sequence	1						2			

The same uni-variable and multi-variable analyses were repeated as above to understand the effect of temperature on haemodynamic variables during the rise in temperature to 38°C and above.

Patient consent: Individual patient consent was not sought as the decision to use pulse contour analysis was made by the treating clinical team. Confounder data included only routinely measured and recorded clinical data. No patient identifiable information is reported.

5.3.3 Effect of paracetamol on haemodynamic variables

Study design and setting: This was a prospectively analysis of routinely collected patient data using stroke volume estimations from pulse contour analysis for patients admitted to PICU/NICU and received paracetamol during this period.

Population: The same population as above (in 5.3.2) were used to study the effect of paracetamol on haemodynamic variables i.e. children who underwent continuous cardiac output monitoring for a period of their admission, over a 12-month period (October 2014-15) on the PICU/NICU at Great Ormond Street Hospital AND had paracetamol at the time of monitoring.

Data sources and variables: Data were collected from the LiDCORapid as described in 5.3.2. Paracetamol data including the dose, route and time of dose were collected from the electronic health record, along with confounder data described in 5.3.2.

Both enteral and intravenous paracetamol doses were considered. The indication for paracetamol was not recorded, with no data available for this retrospectively. The specific dose per kilogram of body weight for each dose of paracetamol were not collected, although all doses were between 10-15 mg/kg. Children on external cooling mattresses were included, provided the mattress temperature was not changed over the time-period analysed. Data on fan therapy or ice-pack application were not available.

Data were analysed in relation to paracetamol dose at the following time points: the hour before paracetamol administration (T=-1); the hour of paracetamol administration (T=0); and four hours following paracetamol administration (T=1, 2, 3, and 4) (similar to the temperature change analysis in Section 2.3.3). Haemodynamic data were collected directly from the LiDCORapid machines as above. Data points with an unreliable signal were excluded. As above, haemodynamic data were summarised for each hour by using the mean value of 200 measurements around the hour mark. Data for the same confounders (adrenaline, noradrenaline, dopamine, dobutamine, milrinone and vasopressin doses, and categorical data for sedation, furosemide, fluid, mean airway pressure and physiotherapy) were collected for the time points T=-1, 0, 1, 2, 3 and 4.

Study size: An a priori sample size calculation was not undertaken, although data from a minimum of 20 patients were expected to be collected in a 12-month period.

Data analysis: Repeated measures analysis of variance (ANOVA) was used to analyse the effect on HR, SVI, CI, SVRI and MBP of time in relation to paracetamol dose. Multi-level linear regression modelling was used for multi-variable analysis, with (a) MBP, HR, SVI, CI or SVRI as dependent variables (i.e. 5 separate models); (b) time, expressed as hours from the paracetamol dose (i.e. -1, 0, 1, 2, 3, 4), along with the above confounders as fixed effect variables, and (c) each dose administration and patient as random effect variables. This enabled us to evaluate changes in MBP, HR and SVI in relation to the time from the paracetamol dose, evaluating the effect per dose, per patient. This controlled for the assumption that each patient may not have the same haemodynamic effect with paracetamol as another, and the effect may vary between doses in the same patient. Each patient therefore was their own control, with a comparison made before and after paracetamol.

Data for CVP were not measured real-time. Although this would have a modest effect on SVRI, to verify this the effect of SVRI on changes in MBP due to paracetamol were evaluated alternatively. Assuming the greatest MBP change occurred at T=2 (i.e. 2 hours

post paracetamol dose), as per Schell-Chaple et al [Schell-Chaple 2017], linear regression was used to examine the effect of HR and SVI on MBP from the coefficient of determination (adjusted R^2 , the proportion of change in MBP explained by the changes in HR and SVI). From this the relative effect of SVRI on MBP (i.e. $1-R^2$) could be inferred.

As paracetamol was not only used for children with fever, the effect of paracetamol on febrile and non-febrile children were explored by comparing nested models, with or without a binary fever variable (fever=0 if afebrile, 1 if febrile) as an interaction term for the time in relation to paracetamol dose. The two models were compared using the log-likelihood ratio test.

Patient consent: These the data were a subset of the data used to test the effect of temperature on haemodynamic variables, therefore individual patient consent was not sought for the same reasons.

All data were analysed using Microsoft Excel (Microsoft Corp. WA, USA) and R (www.cran.r-project.org). All visual basic and R code used are detailed in Appendix C.

5.4 Results

5.4.1 Effect of temperature on heart rate and blood pressure in PICU using continuous temperature data

A total of 1014 children were admitted in the calendar year of 2016 to P/NICU. Of these, 213 children were identified as having continuous temperature monitoring during their admission over the 12-month period from the electronic health record. Data were excluded if the temperature data were not labelled as 'core', 'oesophageal', 'rectal' or 'bladder', to avoid the use of continuous skin temperature. Following exclusion, data were available from 170 admissions (79%). The median age was 20 months, with the inter-quartile range 1-57 months, and total range 0-193 months (0-16 years). The rest of the baseline characteristics

are shown in Table 5.1. The age distributions of the children are shown in are shown in Figure 5.3.

Baseline characteristics	Total (n=170)
Age in months, median (IQR)	20 (1-57)
Prematurity	
<37 weeks CGA	33 (19.4)
<27 weeks CGA	7 (4.1)
Male, n (%)	107 (62.9)
Planned admission, n (%)	17 (10)
PIM % risk of mortality, median (IQR)	4.6 (2.7-9.7)
Categories of risk of mortality, n (%)	
<1%	13 (7.6)
1-5%	84 (49.4)
5-15%	46 (27.1)
>15%	30 (17.6)
Organ support, n (%)	
Mechanical ventilation	164 (96.5)
Vaso-active drugs	87 (51.2)
Continuous renal replacement therapy	28 (16.5)

Table 5.1: Baseline characteristics of children with available continuous temperature monitoring data admitted to P/NICU over a 12-month period. Continuous temperature monitoring was applied for all or part of the admission. Organ support data is for the entire admission and may not correspond to the time of continuous data monitoring.

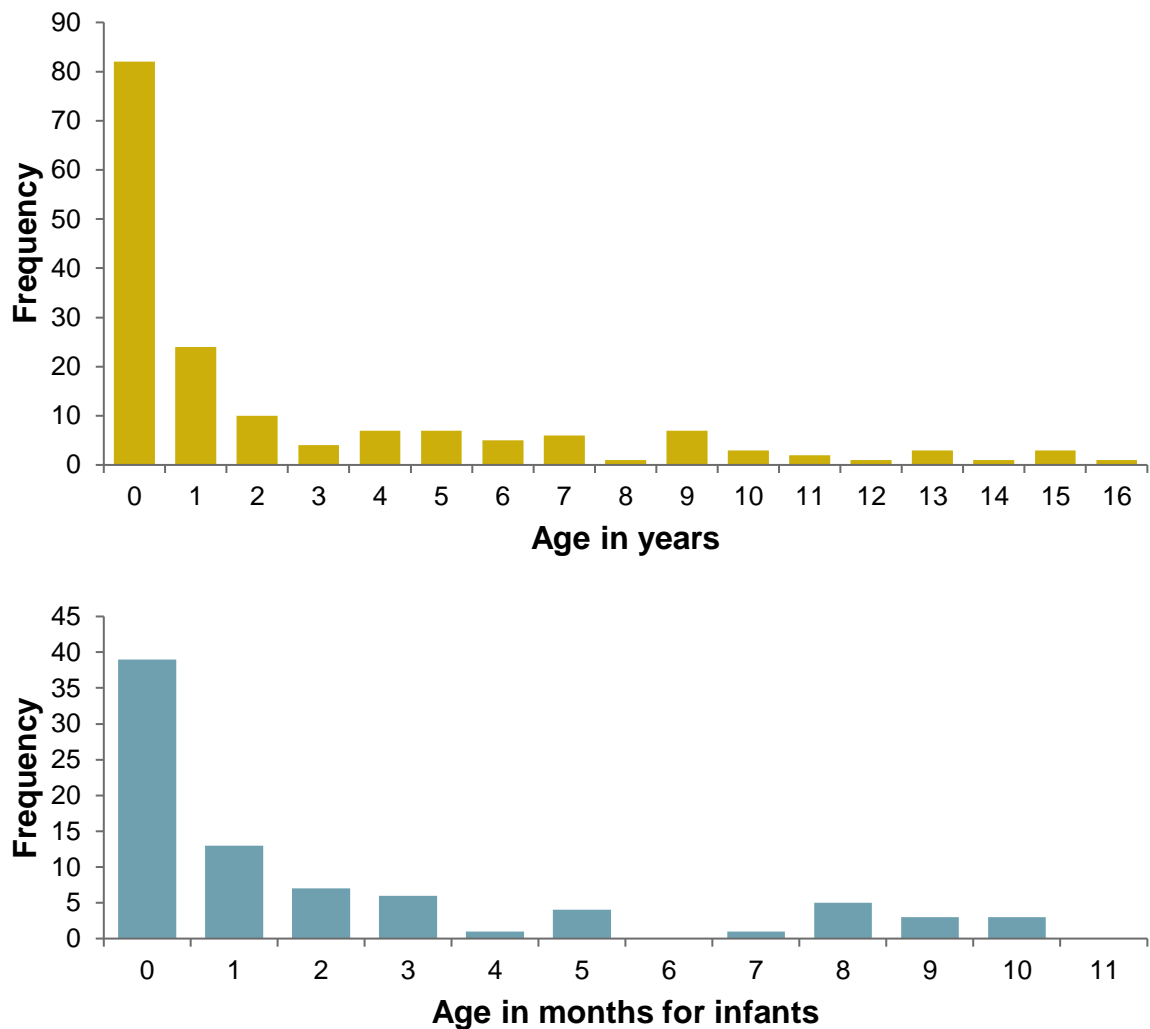


Figure 5.3: Age distribution of children with continuous temperature measurements (n=170). The top panel shows the distribution in years, the bottom panel shows the distribution of those <1 year in months.

A total of 7,535,917 data-points were available for analysis. Temperature values less than 32°C were excluded as spurious (44,139 measurements excluded, 0.6% of total data).

There were 7,394,466 heart rate measurements available for analysis. The median heart rate was 126 beats/min (inter-quartile range 110-141 beats/min). Following multi-level linear regression analysis, the regression coefficient for temperature was 8.31 (95% CI 8.30-8.33) i.e. for 1°C increase in temperature, the mean increase in heart rate was 8 beats/min. The results are summarised in Table 5.2.

Variable	Number of valid measurements	Median	Inter-quartile range	Multi-level linear regression coefficient for temperature	95% CI for regression coefficient
Temperature, °C	7492750	36.8	36.2-37.3		
Heart rate, beats/min	7393294	126	110-141	8.31	8.30, 8.33
Systolic blood pressure, mmHg	5162212	85	72-105	1.13	1.10, 1.16
Diastolic blood pressure, mmHg	5170284	49	42-57	-0.05	-0.06, -0.04
Mean blood pressure, mmHg	5212459	62	54-74	0.11	0.09, 0.12

Table 5.2: Summary statistics for high-resolution continuous bedside monitor data. Data were recorded every 5 seconds. The multi-level linear regression coefficients, with 95% confidence intervals, are shown for temperature. A 1°C rise in temperature increases the corresponding measurement by this amount.

Given the unequal age distribution in the cohort, typical of the PICU population, heart rate values were converted into age standardised z-scores, based on normal reference ranges [Fleming 2011]. The median z- score for heart rate (zHR) was 0.62, with an inter-quartile range of -0.56 to 1.98 (Figure 3.3). The zHR values were then used to evaluate the effect of temperature on zHR as previously described. For each 1°C rise in temperature, the zHR increased by 0.585 (95% CI 0.584-0.586). Therefore, for each 1°C rise in temperature, the heart rate increases by just over half a standard deviation of the distribution for age.

Although Tanner suggested the change in heart rate across the temperature range was linear, figure 5.4 suggests that the heart rate temperature relationship is not linear. Thompson et al found the heart rate change was greatest between 37 and 38°C. To test this, the multi-level linear regression was repeated for temperatures in 1°C intervals from 36°C.

The regression coefficient changed for each temperature interval: between 36-37°C the coefficient was 6.32; for 37-38°C the coefficient was 10.47; for 38-39°C the coefficient was 20.31; for 39-40°C the coefficient was 15.43.

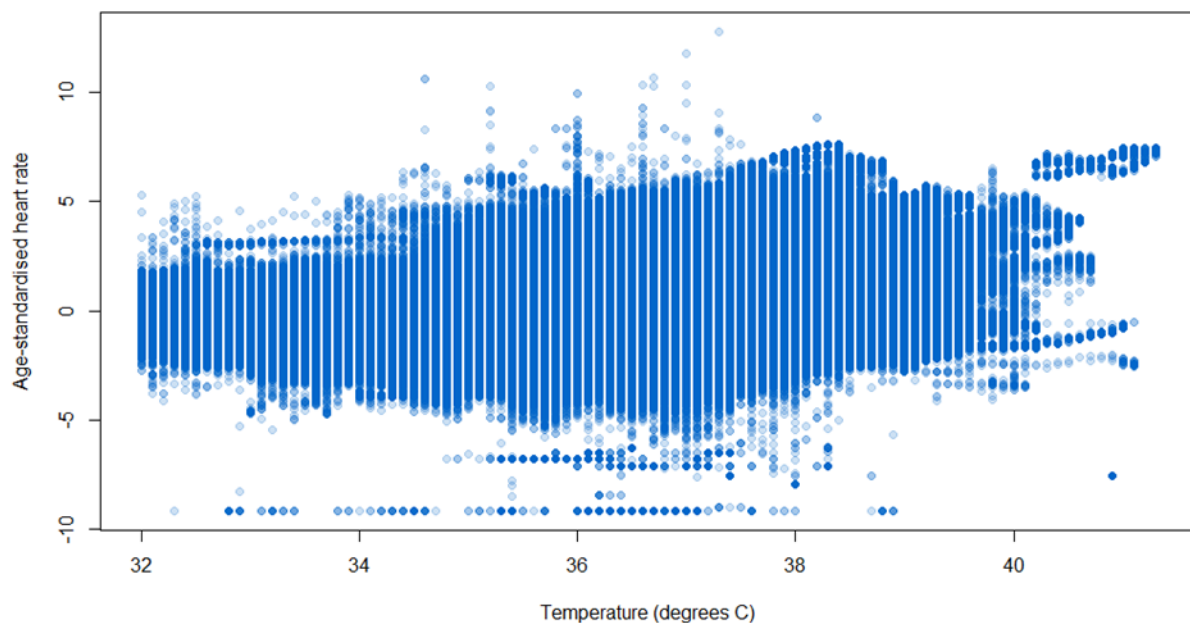


Figure 5.4: Distribution of age-standardised heart rates over the temperature range 32-42°C for 170 admissions to the paediatric intensive care unit. Data are recorded at 5 second intervals, with 7,393,294 heart rate and temperature measurement pairs. Each data-point is a light blue circle, colour density increases when circles are overlaid. zHR increases with temperature, although the effect is more prominent above 35°C.

Therefore, the greatest heart rate change was between 38-39°C, with the heart rate increasing by 20 beats/min for a rise of temperature between 38 to 39°C. It is possible that younger children with higher heart rates had temperatures between 38 and 39°C, thereby increasing the coefficient. To account for this, the analysis was repeated with standardised heart rates: the changes were similar, with the largest coefficient for temperatures between 38 and 39°C. The changes in heart rate and standardised heart rate with temperature are shown in Figure 5.5, with values in Table 5.3.

Temperature intervals	Number of children	Number of observations	Regression coefficient for heart rate (95% CI)	Regression coefficient for zHR
36-37°C	128	3032884	6.33 (6.27-6.39)	0.44 (0.44-0.45)
37-38 °C	127	2488054	10.47 (10.40-10.54)	0.75 (0.75-0.76)
38-39°C	80	535348	20.31 (20.17-20.45)	1.36 (1.36-1.37)
39-40°C	28	74266	15.42 (15.05-15.80)	1.03 (1.01-1.06)

Table 5.3: Table showing changes in heart rate and zHR for each 1°C rise in temperature at different intervals. The greatest increase in heart rate occurs between 38 and 39°C, followed by the increase between 39 and 40°C.

Continuous blood pressure measurements were available for 123 patients. There were 5,212,459 mean blood pressure measurements available for analysis. For mean blood pressure, the median value was 62 mmHg (IQR 54-74 mmHg). The regression coefficient for temperature was 0.11 (95% CI 0.09-0.12). For systolic blood pressure, the regression coefficient for temperature was 1.13 (95% CI 1.10-1.16), and for diastolic blood pressure - 0.05 (95% CI -0.06 to -0.04). The results are summarised in Table 5.2.

The relationship between age-standardised blood pressure and temperature was similarly evaluated. The median z-score for systolic blood pressure was -0.2 (IQR -1.4, 1.4). The regression coefficient for temperature was 0.17 (95% CI 0.17-0.18). The median z-score for diastolic blood pressure was -0.1 (IQR -0.9, 0.6). The regression coefficient for temperature was 0.03 (95% 0.03-0.03). Therefore, both crude blood pressure and z-scores do not change much in relation to temperature.

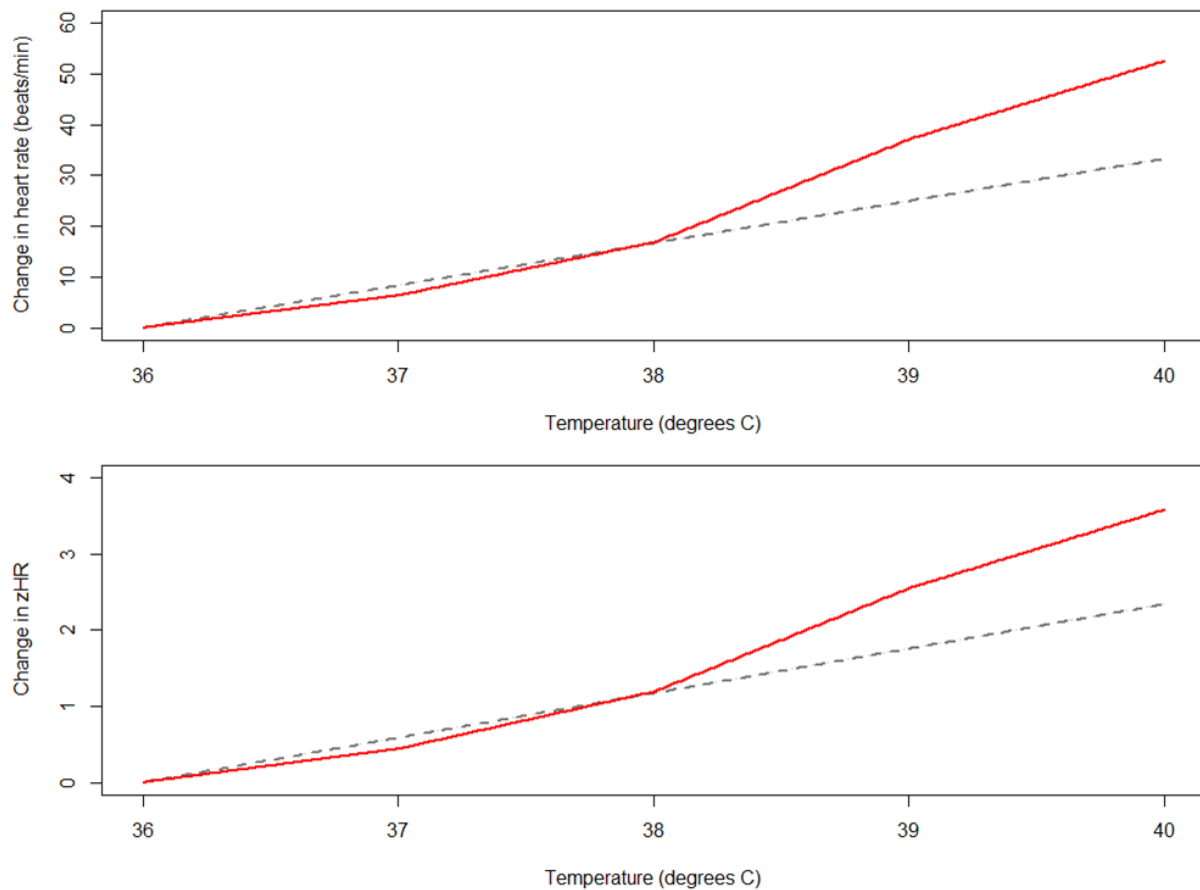


Figure 5.5: Changes in heart rate (top panel) and zHR (bottom panel) over 1°C intervals between 36 and 40°C. The dotted grey line represents the change in heart rate over the temperature range (32-42°C) following multi-level regression of 7,393,328 heart rate and temperature measurements in 170 patients. Separate coefficients were calculated for heart rates for corresponding temperatures between 36-37°C, 37-38°C, 38-39°C and 39-40°C, plotted in red. The changes are similar for zHR, suggesting that the larger coefficient for 38-39°C was not secondary to younger children with higher heart rates having temperatures between 38-39°C.

Like heart rate, the blood pressure and temperature relationship was not linear but temperature sensitive. When the regression analysis for mean blood pressure is repeated for 1°C intervals of temperature between 36 and 40°C, the regression coefficients vary: between 36-37°C the regression coefficient is 0.09 (95% CI 0.03-0.15); between 37-38°C it is 2.24 (95% CI 2.17-2.31); for 38-39°C it is 2.48 (95% CI 2.32-2.64) and for 39-40°C it is 6.01 (95% CI 5.45-6.57). Therefore, for a temperature rise between 39 and 40°C, the mean blood

pressure increased by 6 mmHg, a clinically significant amount. However, the discrepancy between the overall linear coefficient and that at higher temperatures was reflective the small number of children with continuous blood pressure measurements and high temperatures: therefore, these results must be interpreted with caution (Figure 5.6).

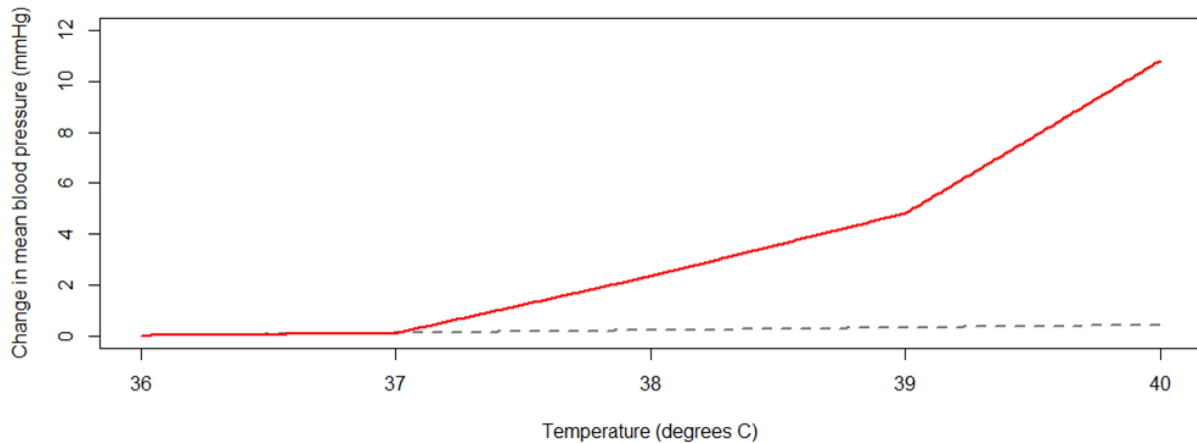


Figure 5.6: Changes in mean blood pressure over 1°C intervals between 36 and 40°C.

The dotted grey line represents the change in blood pressure over the temperature range (32-42°C) following multi-level regression of 5,212,549 continuous blood pressure and temperature measurements in 123 patients. Separate coefficients were calculated for heart rates for corresponding temperatures between 36-37°C, 37-38°C, 38-39°C and 39-40°C, plotted in red. The overall regression line reflects that of the 36-37°C interval, reflecting that most blood pressure measurements were at lower temperatures.

5.4.2 Effect of temperature and fever on advanced haemodynamic variables

Data were available from 38 patients admitted to PICU. The admission characteristics of the patients are shown in Table 5.4. Fifty-five separate calibration episodes were undertaken – data from each of these were analysed separately. The total number of data-points available for analysis was 1522. The median number of temperature recordings for each calibration episode was 15 (range 1-123). The calibration episode with a single data-point did not contribute to uni-variable analyses.

The mean values for the haemodynamic variables in the population were as follows: HR 130.9 beats/min, SVI 31.0 ml/m², CI 4.1 L/min/m², SVRI 1581.4 dynes/cm⁵/m².

The Spearman correlation coefficient between temperature and HR, SVI, CI, SVRI and MBP were calculated for each calibration episode. The median correlation coefficients and inter-quartile ranges are shown in Table 5.5. The scatter plots for the correlation coefficients for each calibration episode is shown in Figure 5.7.

Heart rate showed the best correlation with temperature compared to the other haemodynamic variables. Even for heart rate however, the correlation was poor, with a median coefficient less than 0.5.

For multi-variable analysis, only data available for consecutive hours of data were used as described above. Ninety-eight consecutive hour sequences were identified for 37 patients, with a total of 1257 data-points. The median number of hours per sequence was 4 (range 2-78). Temperature was normally distributed with a mean of 37.26°C (SD 0.95°C)

The coefficient for temperature for each of the multi-level linear regression models (HR, SVI, CI, SVRI and MBP) are shown in Table 5.6. For each 1°C rise in temperature, HR increased by a mean of 8.19 beats/min, SVI increased by 0.66 ml/m², CI increased by 0.36 L/min/m², and SVRI decreased by 153.61 dynes/cm⁵/m². MBP did not change significantly. Considering the mean values for the haemodynamic variables from the data, the effect of temperature was greatest on SVRI: a 1°C rise in temperature on average was associated with a fall in SVRI by 9.6%, an increase in HR by 6.1%, SVI by 2.2% and CI by 8.8%. This suggests that the SVRI fell as the CI increased to maintain a stable blood pressure.

Table 5.4 (overleaf): Characteristics of children with cardiac output monitoring used to analyse the effects of temperature on advanced haemodynamic variables. Weight was either measured or estimated. Body surface area was calculated using weight and height data (as calculated by the LiDCOrapid pulse contour analyser).

Patient number	Weight (kg)	Body surface area (m ²)	Age (months)	Diagnosis	Maximum temperature (°C)
1	65	1.69	167	ARDS	39.1
2	45	1.27	147	OOHCA, septo-optic dysplasia	39.8
3	22	0.83	95	Sepsis	39.2
4	13.3	0.59	37	RSV bronchiolitis/pneumonia	40.4
5	11.1	0.53	22	Pancreatitis, propionic acidaemia	38.4
6	72	1.87	181	Post op bowel resection, Crohn's disease	38
7	11.3	0.49	26	Pneumonia, ependymoma	38.4
8	8.1	0.36	18	Metapneumovirus pneumonia	39.8
9	8	0.34	18	Acute typhilitis, congenital pancytopenia	39.7
10	11.4	0.48	26	CMV infection, SCID	38.4
11	5.1	0.31	8	Bronchomalacia, Pentalogy of Cantrell	37.8
12	10	0.49	11	Sepsis, ATRT	37.3
13	18	0.74	64	Appendicitis	40
14	4	0.24	0	Sepsis	38.9
15	5.5	0.26	1	Bronchiolitis	38.8
16	15	0.64	49	Pneumonia	40
17	28.5	1.05	123	Sepsis	40.5
18	8	0.37	6	Bronchiolitis	37.7
19	8	0.38	6	Sepsis, ATRT	37.7
20	19.2	0.76	80	Sepsis, HLHS	39.5
21	8.8	0.41	15	Pneumonia	39.4
22	60	1.6	172	Post renal cell carcinoma resection	38.5
23	65	1.71	166	Status asthmaticus	38.6
24	25.5	0.98	83	Status asthmaticus	38.7
25	28	0.98	89	OOHCA	39
26	29.3	0.88	53	Influenza ARDS	37.7
27	11.2	0.48	18	Influenza, aplastic anaemia	37.5
28	3.6	0.22	1	Sepsis	38.3
29	10	0.45	14	Empyema	39.1
30	14	0.58	35	Aspiration pneumonia, status epilepticus	38.2
31	3.1	0.2	0	Necrotising enterocolitis	36.4
32	56	1.72	180	Intracranial empyema	38.5
33	50	1.49	138	Vasculitis	37.7
34	5.3	0.27	2	Post-pancreatectomy	38.7
35	9.5	0.43	6	OOHCA	37.8
36	58	1.56	128	Sepsis	38.8
37	20	0.79	53	Sepsis	36
38	17.5	0.74	58	Sepsis	38.8

	Median correlation coefficient	25 th centile of correlation coefficients	75 th centile of correlation coefficients
Heart rate	0.45	0.25	0.65
Stroke volume index	0.06	-0.18	0.36
Cardiac index	0.25	0.04	0.50
Systemic vascular resistance index	-0.24	-0.47	0.12
Mean arterial pressure	0.06	-0.18	0.36

Table 5.5. Summary statistics for the Spearman correlation coefficients of temperature and haemodynamic variables for the 55 calibration episodes from 38 patients. Heart rate showed weak correlation with temperature, with the rest of the haemodynamic variables showing poor correlation.

The above analysis assumed that absolute body temperatures have a standard haemodynamic response across a range of temperatures. As evident from the temperature associations with heart rate in Section 5.3.1, there is a difference between temperatures in the fever range compared to normal body temperature. To analyse the haemodynamic effect of fever, particularly during the temperature rise phase of fever, the data were divided by periods of continuous temperature rise, up to and above 38°C.

Data were available from 27 patients who had fever, with 105 periods of rising temperature. The total number of data-points available was 315. The median number of temperature recordings for each period of temperature rise was 3 (range 2-11).

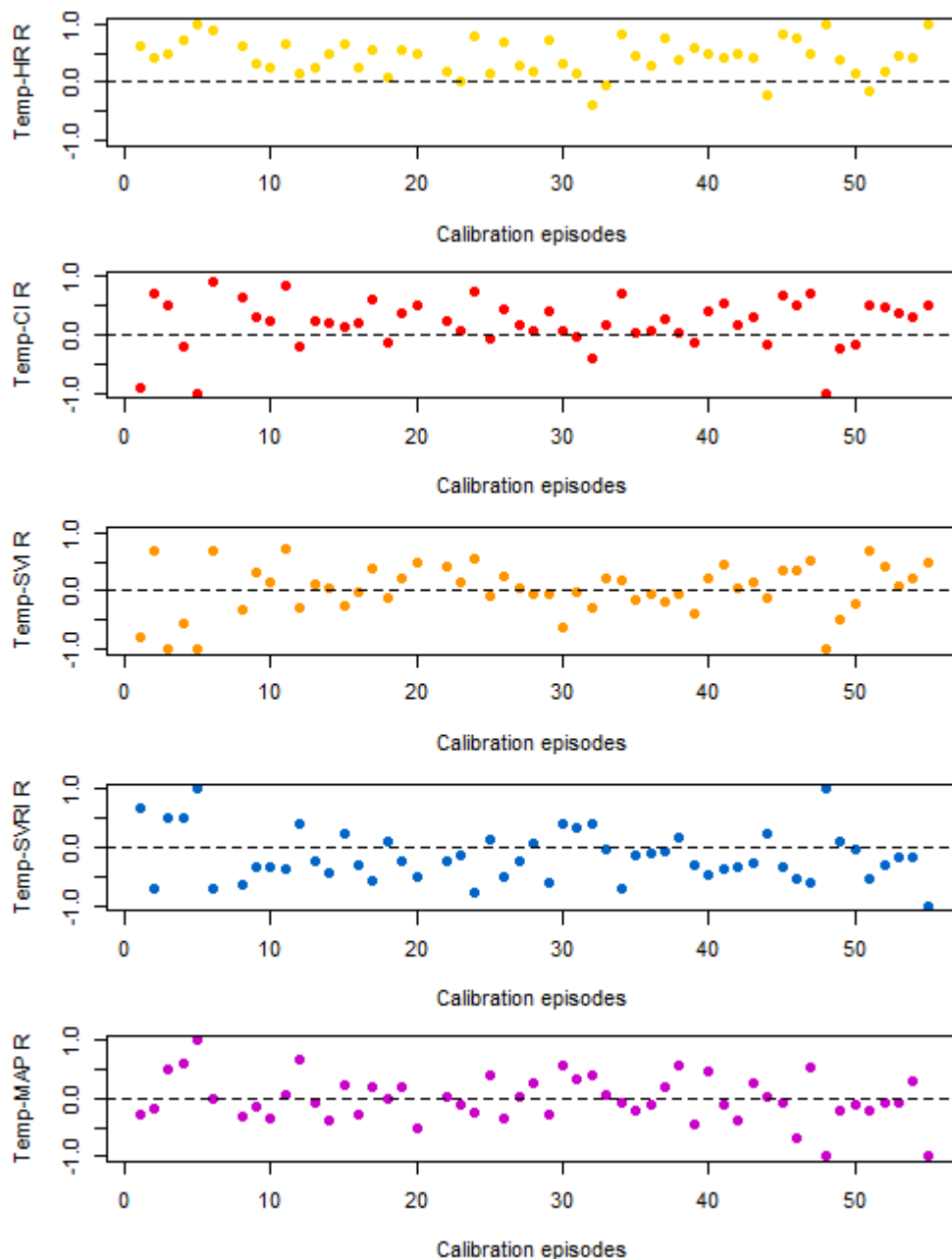


Figure 5.7: Scatter plot of correlation coefficients for each of the haemodynamic variables and temperature. Each calibration episode is analysed separately: a calibration episode refers to a recording of haemodynamic variables using the LiDCOrapid pulse contour analysers between calibration of the cardiac output (using suprasternal Doppler measurements). The correlation coefficients (R) for temperature and heart rate (Temp-HR, *yellow*), stroke volume index (Temp-SVI, *orange*), cardiac index (Temp-CI, *red*), systemic vascular resistance index (Temp-SVRI, *blue*) and mean arterial pressure (Temp-MBP, *purple*) are plotted A-E. The dotted line represents a correlation coefficient of 0 i.e. no correlation between variables. While HR shows moderate correlation with temperature in many episodes, overall the correlation is weak. The other haemodynamic variables show poor correlation.

	Linear regression coefficient for temperature	2.5 th percentile for temperature coefficient	97.5 th percentile for temperature coefficients
Heart rate	8.19	7.26	9.13
Stroke volume index	0.66	0.25	1.08
Cardiac index	0.36	0.28	0.43
Systemic vascular resistance index	-153.61	-234.07	-72.75
Mean arterial pressure	0.30	-0.35	0.96

Table 5.6: Coefficients for temperature from multi-level linear regression models for advanced haemodynamic variables with 95% confidence intervals. Heart rate (HR), stroke volume index (SVI), cardiac index (CI), systemic vascular resistance index (SVRI) have coefficients which are statistically significant at a p-value<0.05 i.e. temperature is independently associated with HR, SVI, CI and SVRI. For mean arterial pressure there is no such association with temperature.

The Spearman correlation coefficient between temperature and HR, SVI, CI, SVRI and MBP were calculated for each calibration episode. The median correlation coefficients and inter-quartile ranges are shown in Table 5.7. The scatter plots for the correlation coefficients for each calibration episode is shown in Figure 5.8.

	Median correlation coefficient	25 th centile of correlation coefficients	75 th centile of correlation coefficients
Heart rate	0.77	0.20	1.00
Stroke volume index	0.41	-0.80	0.87
Cardiac index	0.74	-0.16	1.00
Systemic vascular resistance index	-0.50	-0.90	0.70
Mean arterial pressure	-0.09	-0.80	0.87

Table 5.7: Summary statistics for the Spearman correlation coefficients of temperature during fever and advanced haemodynamic variables. The table shows the correlation coefficients with the 25th -75th centiles for the 105 periods of rising temperature up to and above 38°C from 27 patients. Heart rate and cardiac index showed strong correlation with temperature, with the rest of the haemodynamic variables showing poor correlation.

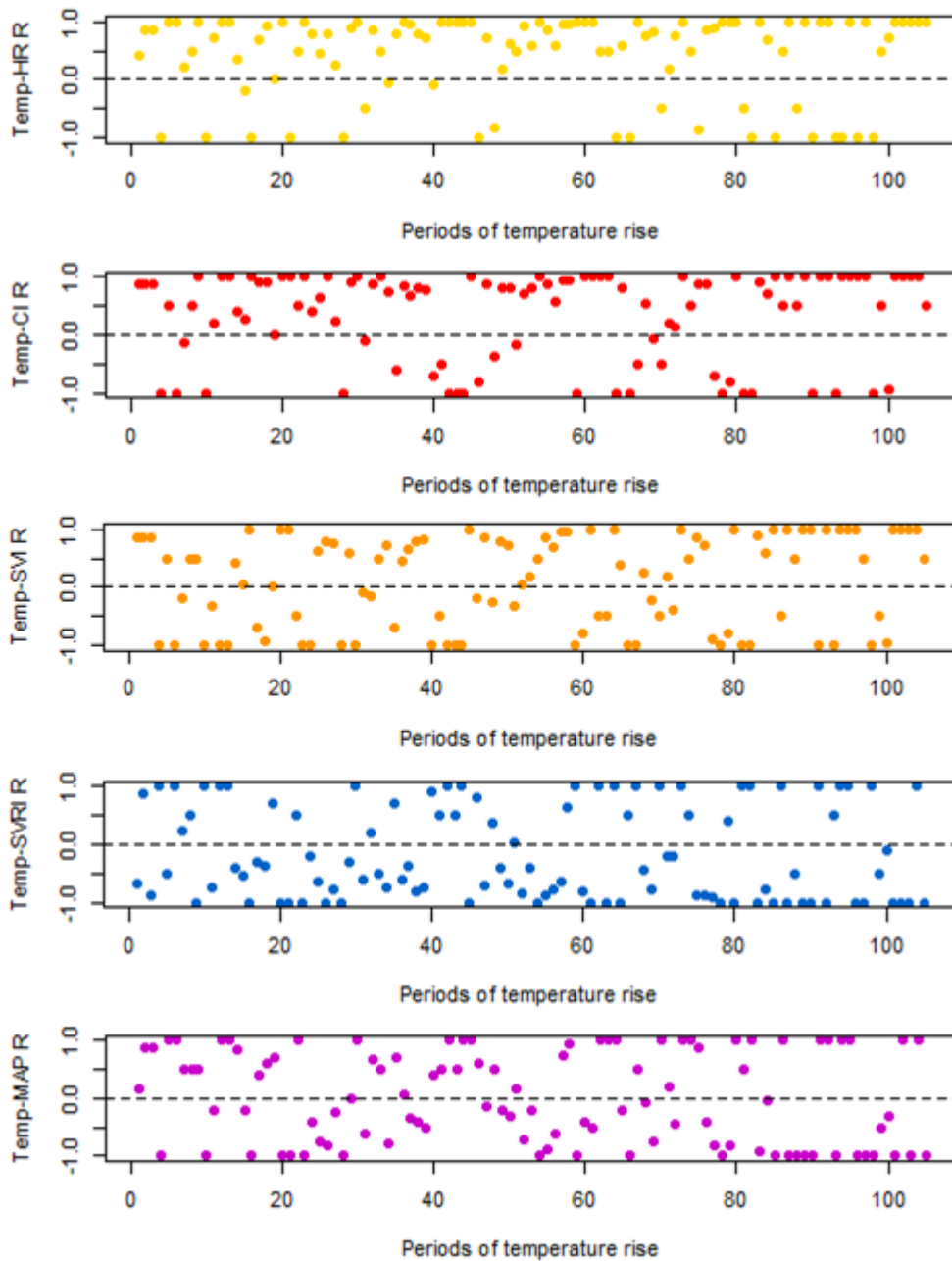


Figure 5.8: Scatter plot of correlation coefficients for each of the haemodynamic variables and temperature for periods of rising temperature $\geq 38^{\circ}\text{C}$. Only periods with a consistent rise in temperature up to and above 38°C were included ($n=105$, 27 patients). The correlation coefficients (R) for temperature and heart rate (Temp-HR, *yellow*), stroke volume index (Temp-SVI, *orange*), cardiac index (Temp-CI, *red*), systemic vascular resistance index (Temp-SVRI, *blue*) and mean arterial pressure (Temp-MBP, *purple*) are plotted A-E. The dotted line represents a correlation coefficient of 0 i.e. no correlation between variables. HR and CI now show good correlation with temperature with a median correlation coefficient of 0.77 and 0.74 respectively. The other haemodynamic variables show poor correlation.

HR and CI both showed strong correlation with temperature during the rise in temperature in the fever grade range. SVRI showed moderate negative correlation, in keeping with previous results.

As above, only data available for consecutive hours were used for multi-variable analysis. Data were available for 24 patients, with 80 sequences of continuous temperature rise. The total number of data-points available for analyses was 314, with the median number of temperature recordings for each sequence of continuous temperature rise was 3 (range 2-11). The mean temperature was 38.02°C, with a standard deviation of 0.88°C.

The coefficient for temperature for each of the multi-level linear regression models (HR, SVI, CI, SVRI and MBP) are shown in table 5.8. For each 1°C rise in temperature, HR was associated with an increase by a mean of 7.94 beats/min, CI with an increase by 0.39 L/min/m², and SVRI with a decrease by 190.55 dynes/cm⁵/m². SVI and MBP did not change significantly.

The mean values for the haemodynamic variables in the population were as follows: HR 132.9 beats/min, CI 4.3 L/min/m², SVRI 1564.9 dynes/cm⁵/m². Therefore, on average SVRI decreased by 12.2% for each 1°C rise in temperature, CI increased by 9.0% and HR rose by 6.0%. As with all temperature, in fever the SVRI falls as CI rises, maintaining without a change in MBP.

5.4.3 Effect of paracetamol on haemodynamic variables

Thirty-one children received 148 paracetamol doses during cardiac output monitoring (a subset of the cohort in Section 5.3.2). Median age was 37 months (IQR 18-109 months). One hundred and twenty-seven (85%) doses were intravenous (Table 5.9). Doses ranged from 10-15mg/kg. MBP decreased post-paracetamol, with the nadir at two hours.

	Linear regression coefficient for temperature	2.5 th percentile for temperature coefficient	97.5 th percentile for temperature coefficients
Heart rate	7.94	6.44	9.43
Stroke volume index	0.74	-0.01	1.48
Cardiac index	0.39	0.26	0.52
Systemic vascular resistance index	-190.55	-333.65	-46.65
Mean arterial pressure	-0.89	-1.93	0.15

Table 5.8: Coefficients for temperature during fever from multi-level linear regression models for advanced haemodynamic variables with 95% confidence intervals. The table shows the coefficients with 95th percentile confidence intervals during 105 periods of rising temperature up to and above 38°C. Heart rate, cardiac index and systemic vascular resistance index had coefficients which were statistically significant at a p-value<0.05 i.e. temperature was independently associated with an increase in heart rate and cardiac index and a decrease in systemic vascular resistance index. Stroke volume index and mean arterial blood pressure did not show a significant association with temperature changes in the fever-range.

The distribution of HR, SVI, CI, SVRI and MBP according to the time-points in relation to paracetamol dose are shown in Figure 5.9a-e. The median HR, SVI and CI all decreased from baseline reaching a nadir at 3-hours post paracetamol dose, then returning to baseline. SVRI increased slightly post dose. Following repeated measures ANOVA, significant differences were seen across time points for HR (p=0.0002), SVI (p=0.002), CI (p=5 x 10⁻³) and MBP (p=0.001) but not for SVRI (p=0.63).

Table 5.9 (overleaf): Characteristics of children with cardiac output monitoring given doses of paracetamol. Weight was either measured or estimated. Body surface area was calculated using weight and height data (as calculated by the LiDCOrapid pulse contour analyser). Fever was defined as a temperature ≥ 38°C at baseline. Age is given in months.

Patient number	Weight (kg)	Body Surface Area (m ²)	Fever	Age (m)	Diagnosis	Intra-venous doses of paracetamol	Total paracetamol doses
1	13.3	0.58	Yes	38	RSV bronchiolitis	6	11
2	10.5	0.48	No	26	Pneumonia	1	1
3	11.4	0.48	No	26	CMV pneumonitis	4	4
4	18	0.74	Yes	64	Septic shock, acute appendicitis	7	7
5	4	0.24	No	1	Bronchiolitis	0	2
6	15	0.64	Yes	49	Streptococcal pneumonia	9	9
7	28.5	1.05	Yes	123	Staphylococcal pneumonia	4	4
8	8	0.36	No	6	Bronchiolitis	0	3
9	8.8	0.41	Yes	15	Pneumonia	2	2
10	65	1.71	No	156	Status asthmaticus	3	3
11	9	0.33	Yes	35	Septic shock	10	10
12	28	0.97	Yes	89	Post cardiac arrest, primary cardiac arrhythmia	0	1
13	8.5	0.31	No	8	Pneumonia	5	5
14	10	0.47	No	14	Empyema	1	5
15	29.3	0.88	No	41	Influenza pneumonitis	0	1
16	3.6	0.22	No	1	Group B Streptococcal sepsis	0	3
17	12	0.54	Yes	30	Toxic shock syndrome	3	3
18	65	1.69	Yes	167	ARDS	11	11
19	14	0.57	Yes	37	Aspiration pneumonia	2	2
20	11.2	0.48	No	31	Influenza pneumonitis, aplastic anaemia	11	11
21	60	1.6	No	141	Renal cell carcinoma	6	6
22	11.11	0.52	No	22	Propionic acidaemia	3	3
23	8.1	0.35	Yes	18	Metapneumovirus bronchiolitis	0	2
24	56	1.71	No	180	Subdural empyema	2	2
25	72	1.86	Yes	181	Crohn's disease	3	3
26	45	1.27	Yes	147	Post cardiac arrest	1	1
27	22	0.83	Yes	95	Staphylococcal pneumonia	2	2
28	10	0.49	No	23	Neutropenic sepsis	9	9
29	17	0.76	Yes	75	Haemophagocytic lymphohistiocytosis	10	10
30	5.3	0.26	Yes	2	Sepsis, congenital hyperinsulinism	1	1
31	58	1.57	No	114	Septic shock	11	11

Multi-variable analysis was used to correct for changes in vaso-active inotropic drugs, fluid boluses, sedation changes, furosemide, physiotherapy and route of administration. Heart rate decreased significantly following paracetamol at 2, 3 and 4 hours, with a nadir 3 hours post-paracetamol dose. The magnitude of decrease was small: at 3 hours post-paracetamol heart rate decreased by 3.64 beats/min (95% CI 1.26-6.02 beats/min), or 3.4% from a baseline HR of 135.84 beats/min. SVI decreased significantly at 2 and 3-hours post paracetamol by a mean value of 1.28 ml/min (95% CI 0.38-2.19) at 2-hours post paracetamol, which was the nadir. For a mean baseline SVI value of 33.15 ml/m², this was a decrease 2 hours post paracetamol by 3.9%. There was a significant decrease in CI at hours 2 and 3 post paracetamol. The maximum effect, 3-hours post paracetamol, was a decrease by 0.301 L/min/m² (95% CI 0.15-0.48), a 6.7% decrease in CI. SVRI did not significantly change post paracetamol. MBP decreased significantly at 1, 2 and 3-hours post paracetamol, with a maximum decrease of 3.02 mmHg (95% CI 1.56-4.47 mmHg) 2-hours post paracetamol, 4.4% from the baseline. The changes following multi-level regression modelling are shown in Figure 5.10a-e, with values summarised in Table 5.10.

Figure 5.9a: Bean plots showing distribution of heart rate (HR) at different time-points in relation to the paracetamol dose.

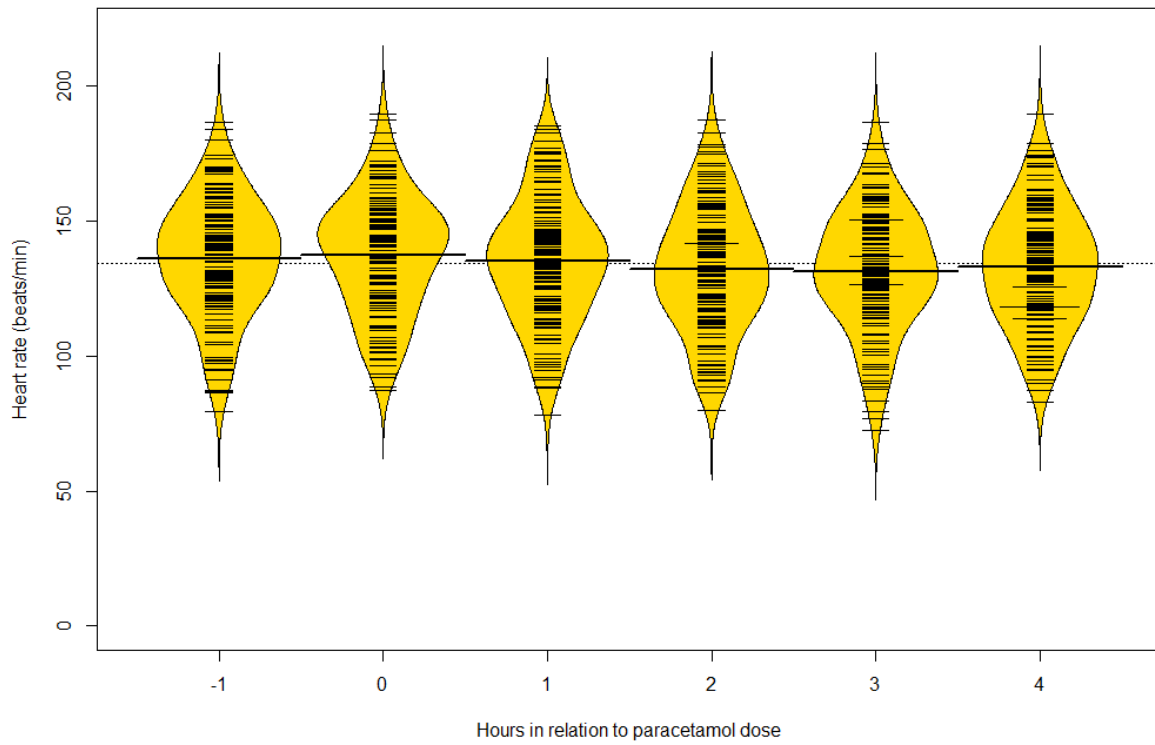


Figure 5.9b: Bean plots showing distribution of stroke volume index (SVI) at different time-points in relation to the paracetamol dose.

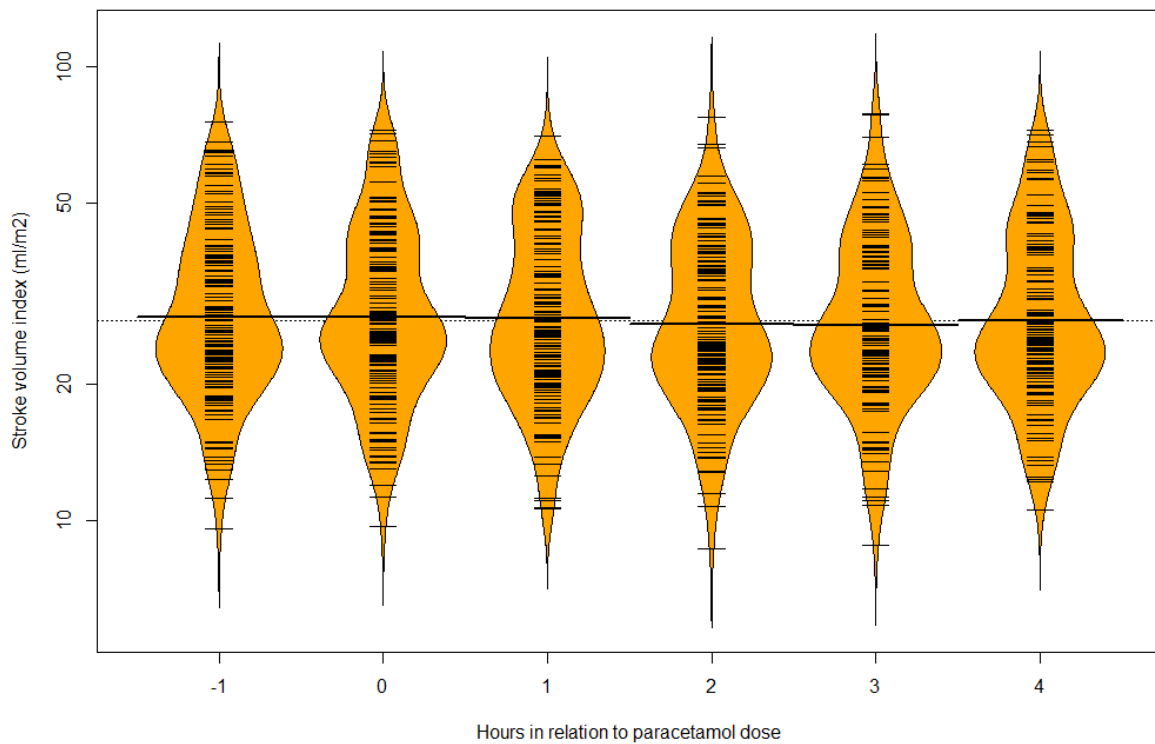


Figure 5.9c: Bean plots showing distribution of cardiac index (CI) at different time-points in relation to the paracetamol dose.

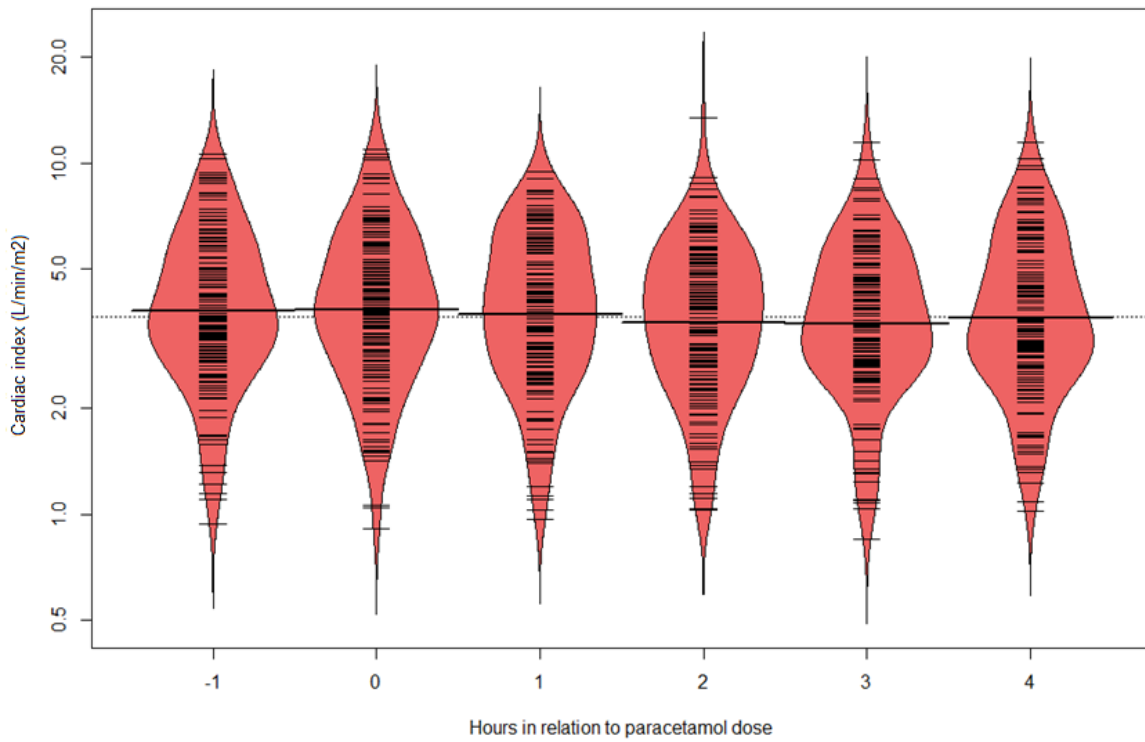


Figure 5.9d: Bean plots showing distribution of systemic vascular resistance index (SVRI) at different time-points in relation to the paracetamol dose.

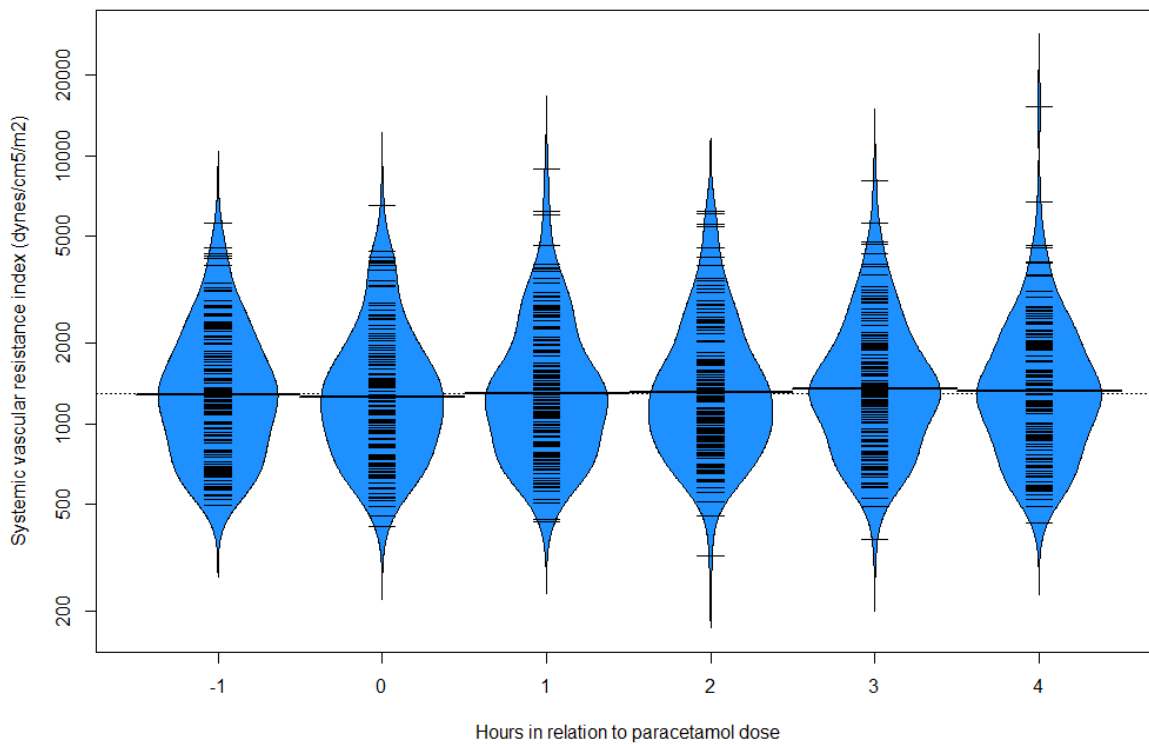


Figure 5.9e: Bean plots showing distribution of mean arterial blood pressure (MBP) at different time-points in relation to the paracetamol dose.

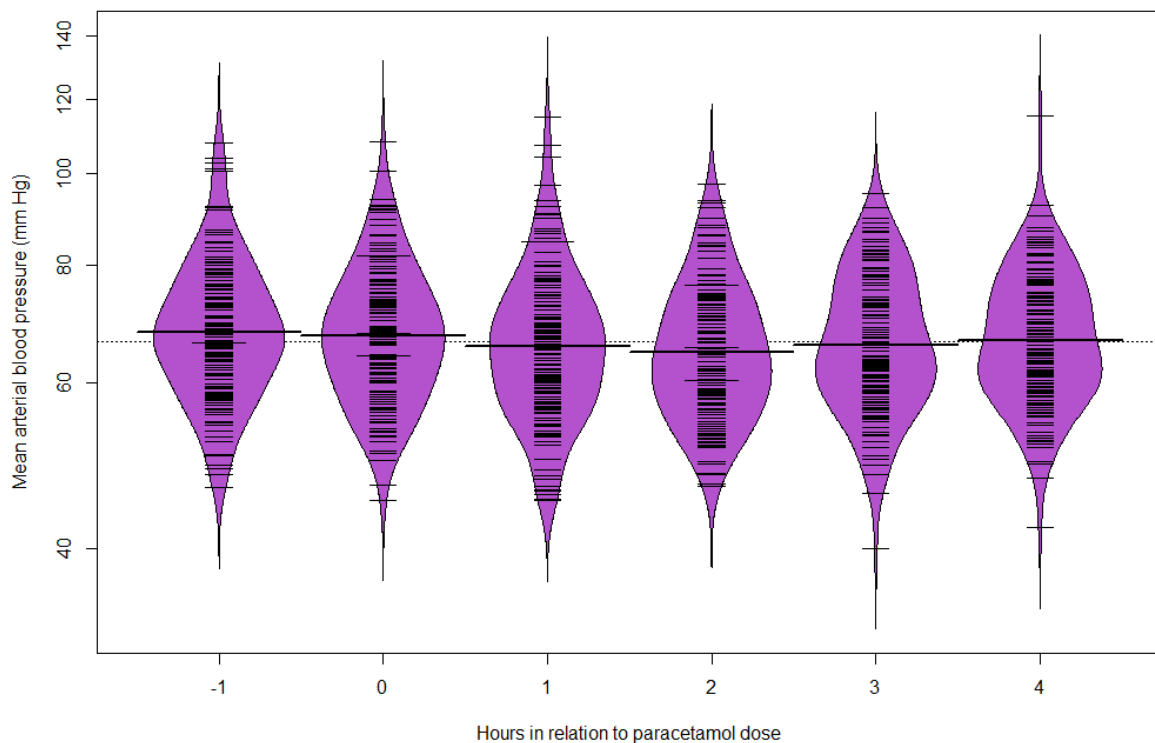


Figure 5.9a-e: Bean plots showing distribution of heart rate (HR), stroke volume index (SVI), cardiac index (CI), systemic vascular resistance index (SVRI) and mean arterial blood pressure (MBP) at different time-points in relation to the paracetamol dose. The paracetamol dose was given at hour 0; the heart rate values in the hour before the dose was given are plotted at time-point -1, and the four hours post dose at time-points 1 to 4. HR, SVI, and CI decreased from baseline, with a nadir 3-hours post-dose, returning towards the baseline thereafter. SVRI increased slightly post-paracetamol; MBP decreased with a nadir at 2-hours post paracetamol.

Figure 5.10a-e: Changes in heart rate (HR), stroke volume index (SVI), cardiac index (CI), systemic vascular resistance index (SVRI) and mean arterial blood pressure (MBP) following paracetamol dose, accounting for confounders using multi-variable analysis. The grey line shows the mean change in each variable, with the shaded area representing the 95% confidence interval. HR and CI decreased following paracetamol dose with the nadir at 3-hours post dose, returning close to baseline by 4 hours. SVI and MBP decreased 2-hours post paracetamol before returning towards baseline by 4 hours. SVRI showed little change post-paracetamol.

Figure 5.10a: Changes in heart rate following paracetamol dose, accounting for confounders using multi-variable analysis.

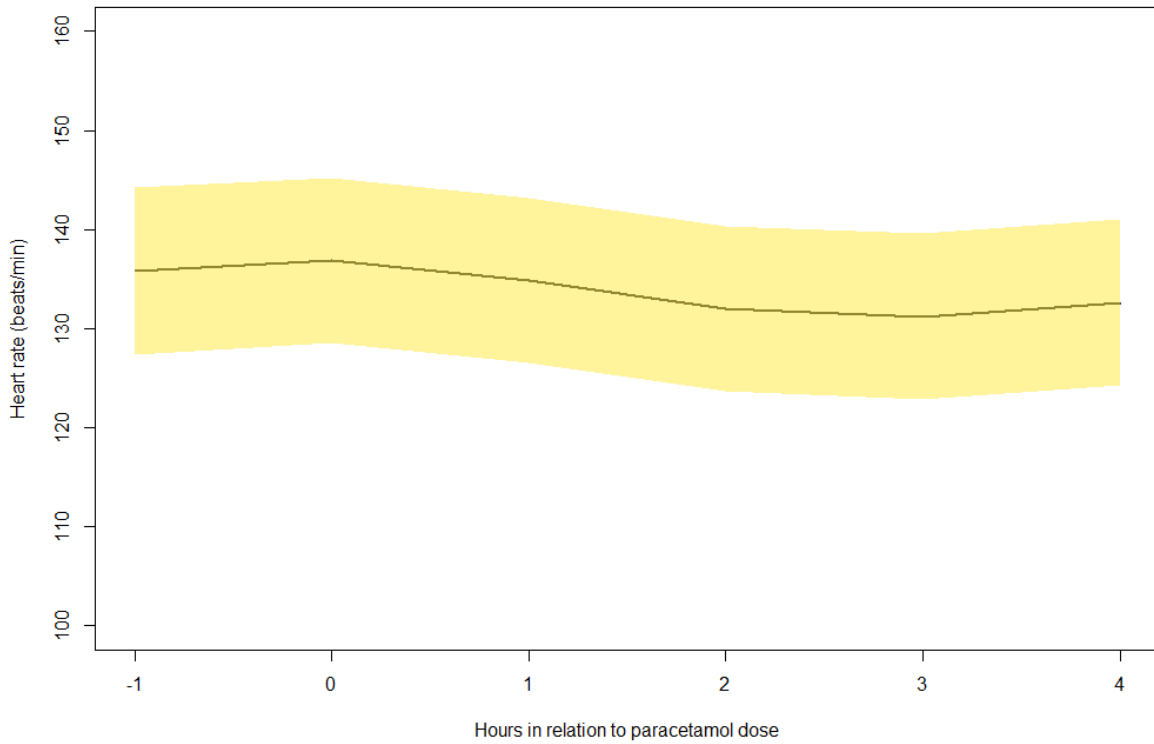


Figure 5.10b: Changes in stroke volume index following paracetamol dose, accounting for confounders using multi-variable analysis.

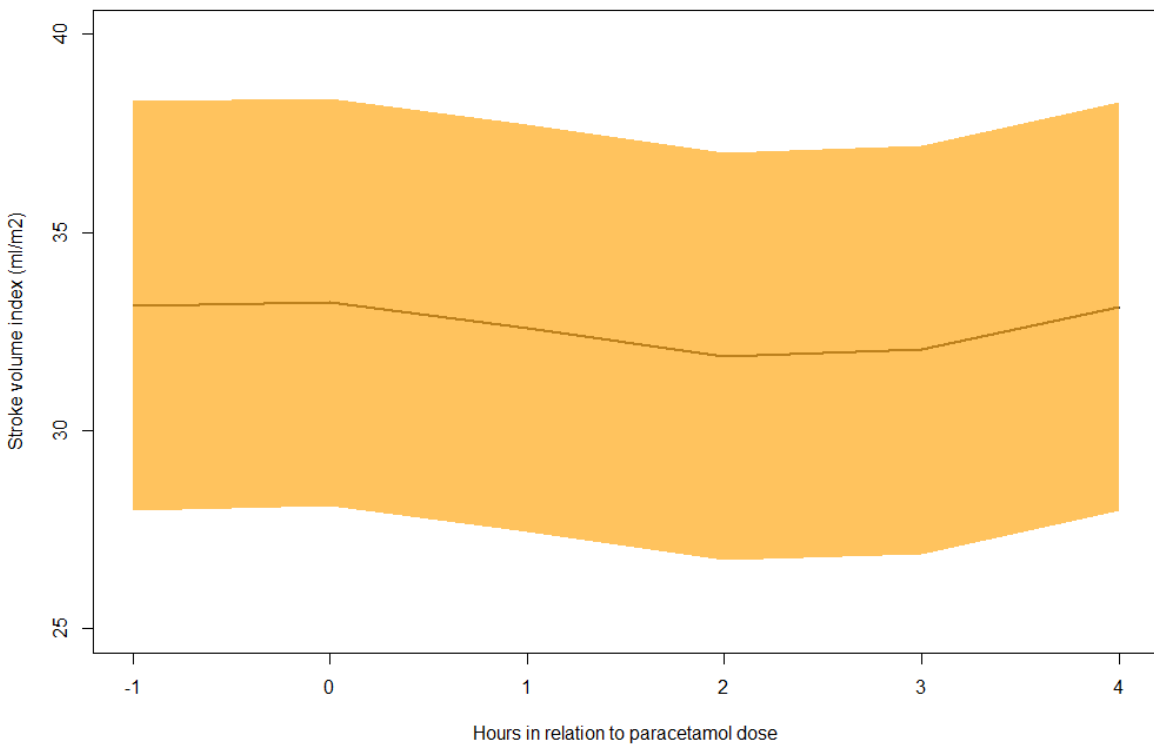


Figure 5.10c: Changes in cardiac index following paracetamol dose, accounting for confounders using multi-variable analysis.

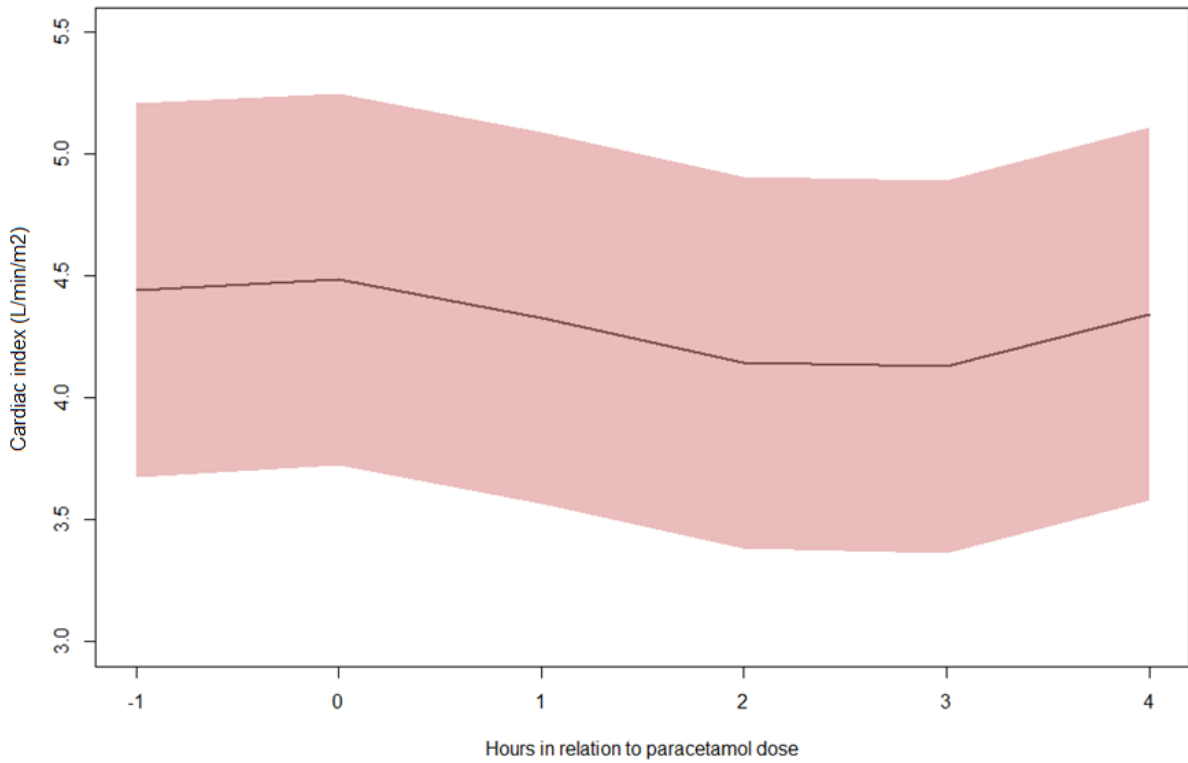


Figure 5.10d: Changes in systemic vascular resistance index following paracetamol dose, accounting for confounders using multi-variable analysis.

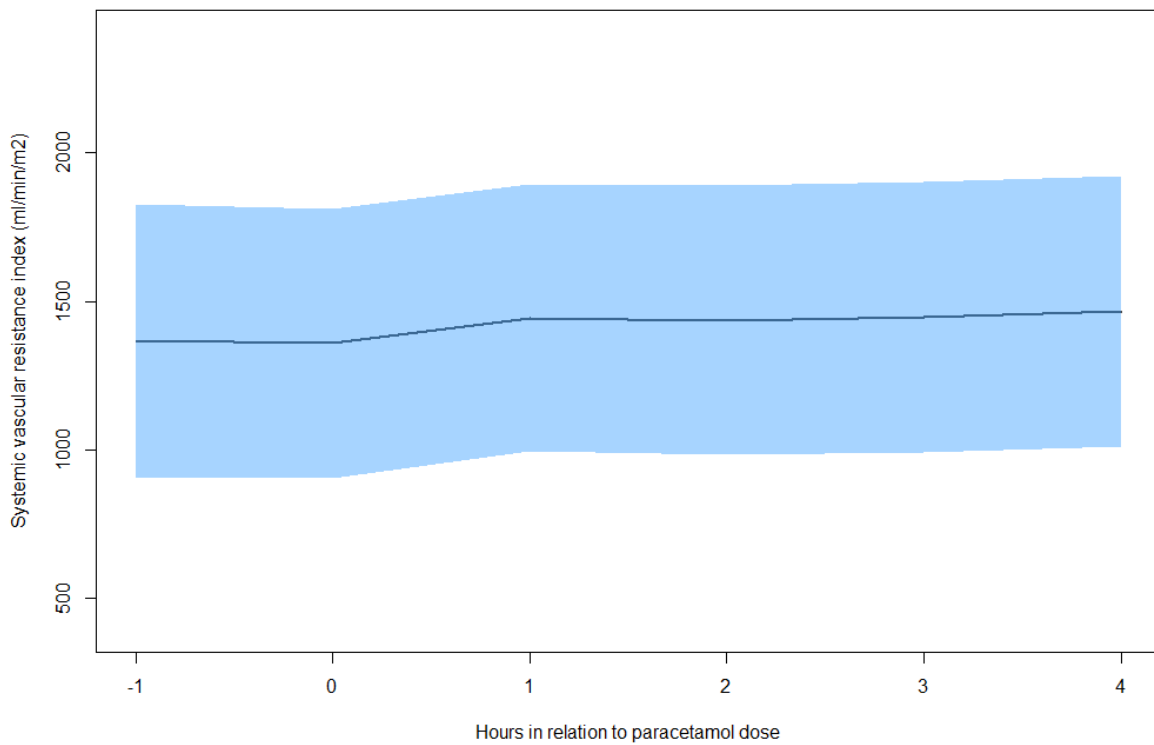
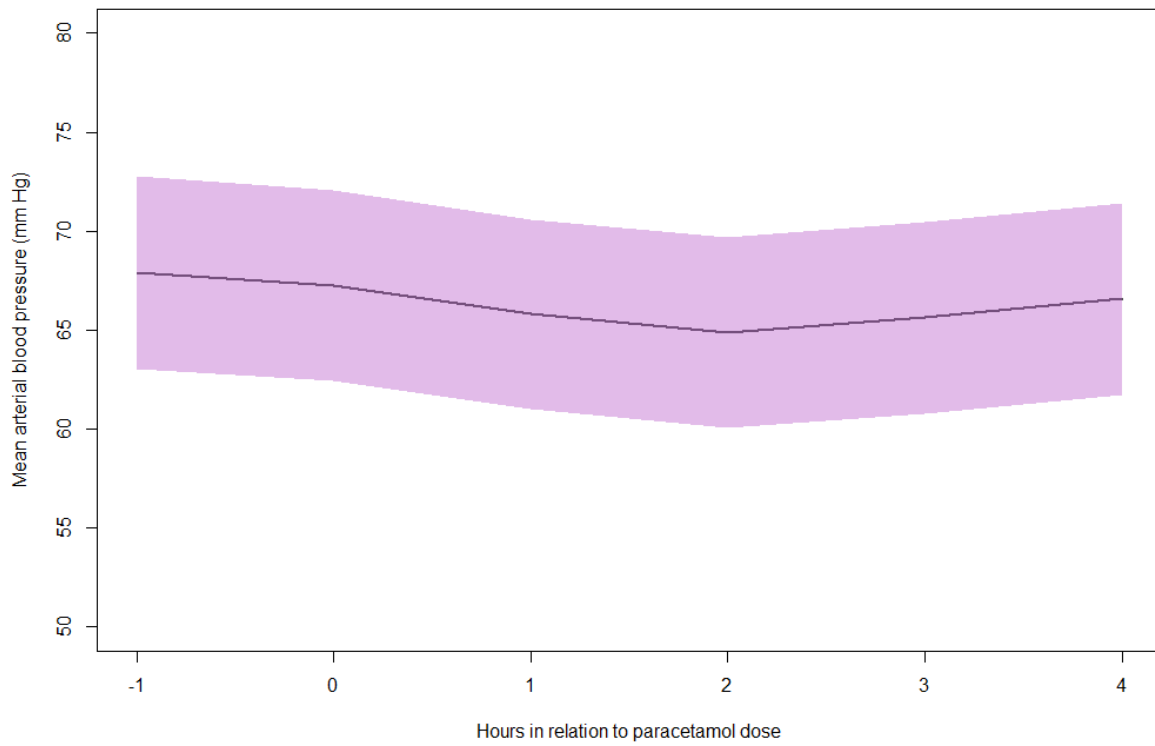


Figure 5.10e: Changes in mean arterial blood pressure following paracetamol dose, accounting for confounders using multi-variable analysis.



Time-points in relation to paracetamol dose (hours)	HR	SVI	CI	SVRI	MBP
-1	135.8 (127.4-144.3)	33.2 (28.0-38.3)	4.44 (3.68-5.21)	1366.5 (907.5-1826.5)	67.9 (63.0-72.7)
0	136.9 (128.5-145.2)	33.2 (28.1-38.4)	4.49 (3.72-5.25)	1358.9 (906.1-1812.6)	67.3 (62.4-72.1)
1	134.8 (126.5-143.2)	32.6 (27.5-37.7)	4.33 (3.57-5.09)	1444.6 (994.2-1896.1)	65.8 (61.0-70.6)
2	132.0 (123.7-140.4)	31.9 (26.7-37.0)	4.14 (3.38-4.91)	1434.9 (981.8-1889.0)	64.9 (60.1-69.7)
3	131.2 (122.8-139.6)	32.1 (26.9-37.2)	4.13 (3.36-4.89)	1446.1 (990.6-1902.6)	65.6 (60.8-70.5)
4	132.7 (124.3-141.1)	33.1 (28.0-38.2)	4.35 (3.58-5.11)	1466.1 (1009.5-1924.3)	66.6 (61.7-71.4)

Table 5.10: Changes in haemodynamic variables in relation to paracetamol. The data are from 148 paracetamol doses given to 31 children who had advanced haemodynamic monitoring at the time. The regression coefficients (95% confidence intervals) for the different time points in relation to a paracetamol dose is shown for heart rate (HR), stroke volume index (SVI), cardiac index (CI), systemic vascular resistance (SVRI) and mean blood pressure (MBP).

Most doses given in this cohort were intravenous (127/148, 85%). Route of administration was included in the above multi-level linear regression analyses as the absorption was likely to affect the peak serum paracetamol levels. However, it is also likely that the time to achieve peak effect was slower with enteral doses – the nadir in blood pressure was at 2 hours with intravenous doses but 3 hours with enteral doses (Figure 5.11). When the same regression analysis was repeated for only the intravenous doses (i.e. excluding the enteral doses), the maximum effect remained similar, with the MBP decreasing by 2.95 mmHg (95% CI 0.27-5.61 mmHg) 2-hours post dose, a decrease of 4.3% from baseline. This reflects the proportion of doses given intravenously.

Most of the described effects of paracetamol on blood pressure have been tested in febrile subjects. Only 54/148 (36%) of doses in this cohort were given when a child had fever (temperature $\geq 38^{\circ}\text{C}$) at baseline (time-points -1 or 0). The multi-level linear regression model for MBP was repeated using fever (as a binary variable, 0 or 1, for each dose) as an interaction term with time-points. This model was compared with the model without fever as a variable using the log-likelihood test: the chi-squared value was 18.2, which was statistically significant (p-value 0.005). This suggests that the change in blood pressure following paracetamol was significantly different in children with fever at baseline when compared to children without fever (Figure 5.12).

Mechanisms affecting blood pressure changes: Changes seen in systolic (SBP) and diastolic blood pressures (DBP) were analysed using multi-level linear regression as above. SBP decreased by 6.7% of baseline 2-hours post paracetamol, whereas diastolic blood pressure decreased by 3.2% of baseline. Therefore, SBP contributes more to the decrease in MBP compared to DBP. Blood pressure is a product of cardiac output and the systemic vascular resistance. To understand the relative effects of cardiac output and systemic vascular resistance on blood pressure, the coefficient of determination (R^2) for the changes in MBP post paracetamol was evaluated following linear regression. Cardiac output is a product of stroke volume and heart rate. The R^2 for HR and SVI (i.e. CI) was only 0.041. This implies only 4% of the variation in the change in MBP post paracetamol could be explained by the variation in change in HR and SVI. The remaining change, i.e. 96%, therefore is likely to be explained by the variation in change in SVRI. When the pulse contour analyser derived SVRI values were used, the R^2 value increased only to 0.25. This would suggest that SVRI has a greater effect on the blood pressure changes compared to cardiac output, but the model fit is fairly poor, possibly due to inaccuracies in measurement.

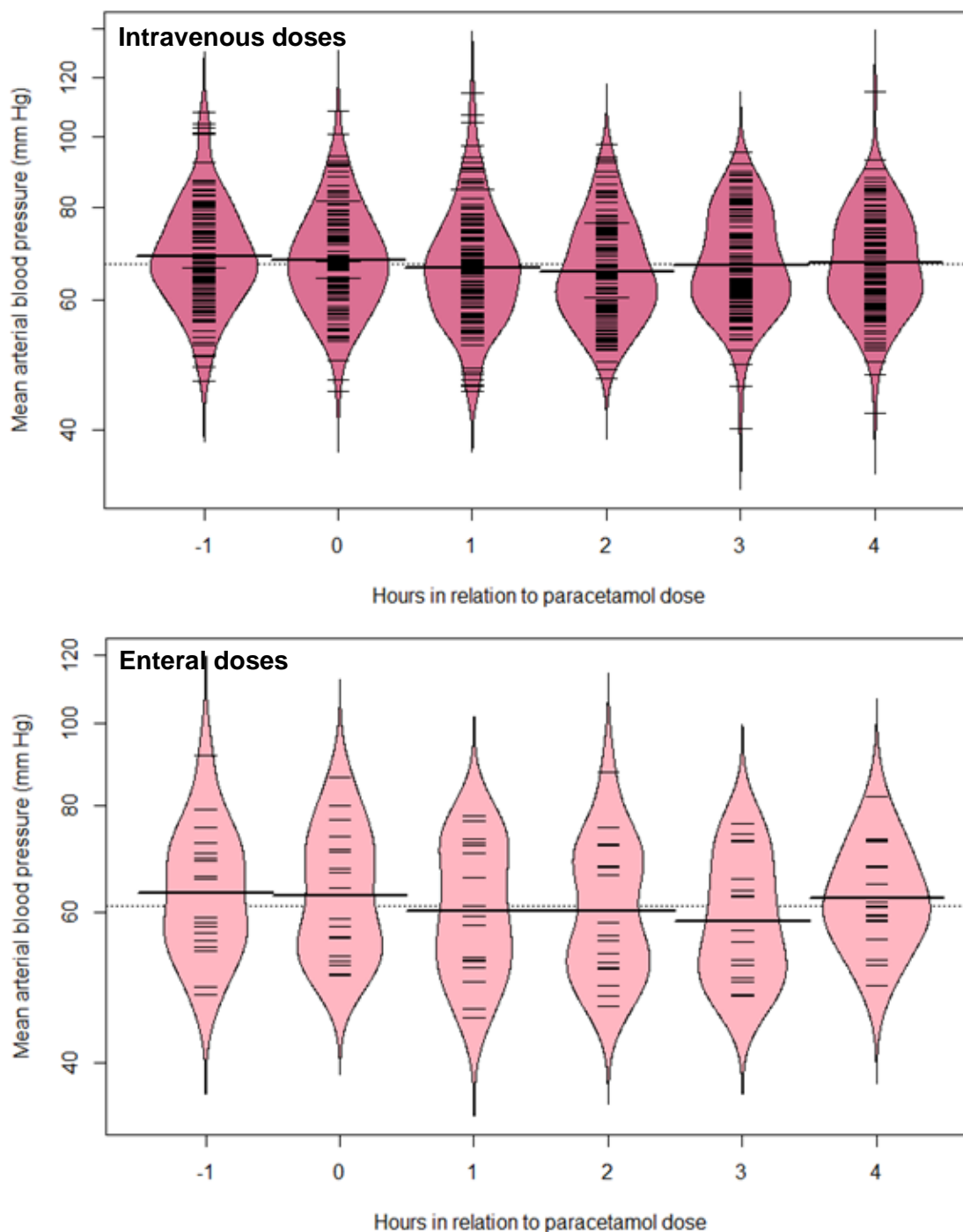


Figure 5.11: Fall in blood pressure post paracetamol in children according to route of admission. Fall in blood pressure post paracetamol in children according to route of administration: top, intravenous doses (n=130); bottom, enteral doses (n=18). The peak effect of paracetamol on blood pressure was at 2 hours following intravenous doses and at 3 hours following enteral doses. Given that most doses in this cohort were given intravenously, the significance of this difference was not investigated further. Both routes were included in subsequent regression models, with route as a confounder variable.

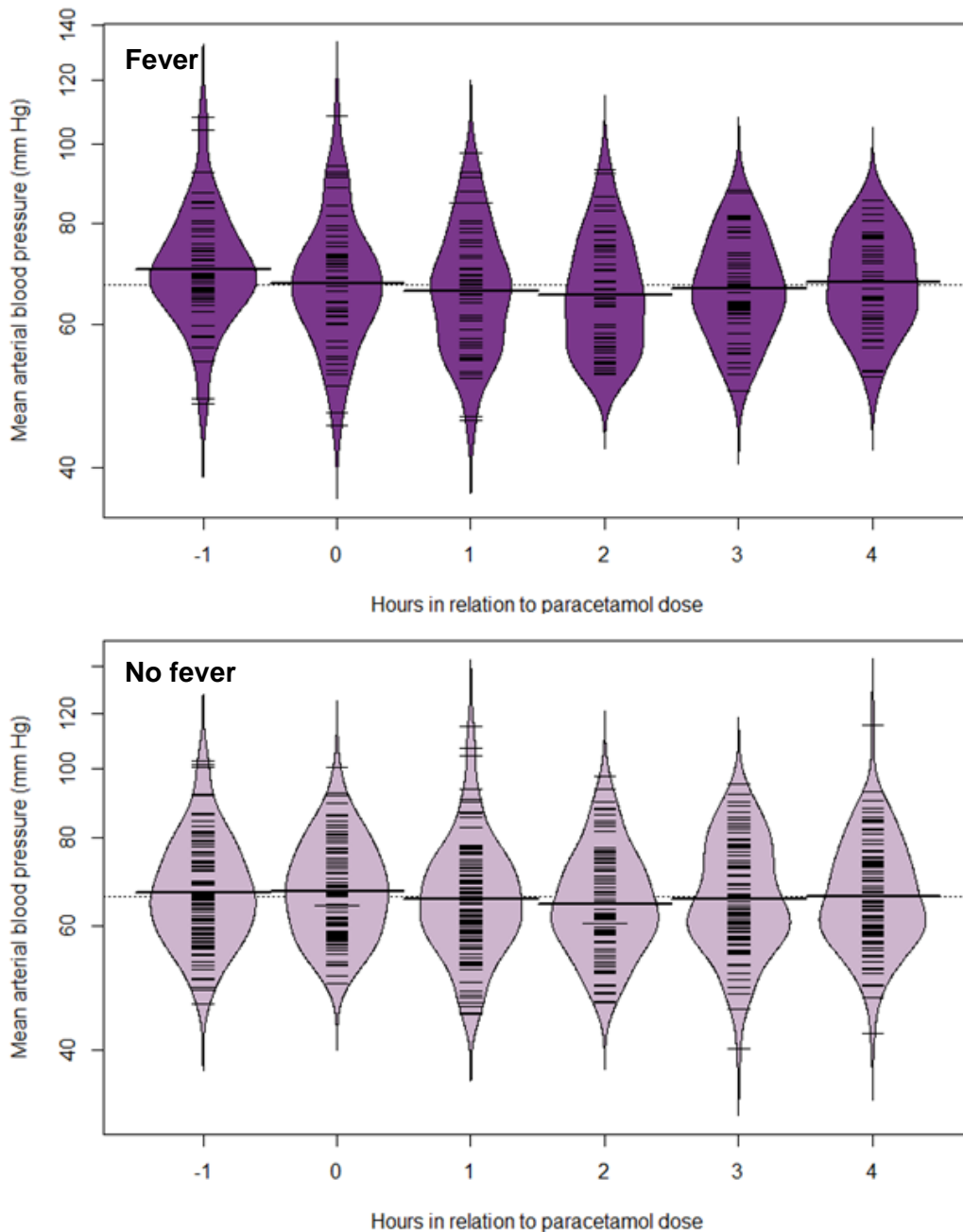


Figure 5.12: Fall in blood pressure post paracetamol in children with and without fever. Fall in blood pressure post paracetamol in children with (top, n=54 doses) and without (bottom, n=94 doses) fever, defined as temperature $\geq 38^{\circ}\text{C}$ at time-points -1 or 0. The decrease in blood pressure is greater in children with fever compared to those without. A multi-level linear regression model, using fever as an interaction term for the time-points, was compared without the fever term, using the log-likelihood ratio test. The chi-squared value was 18.2, which was statistically significant (p -value 0.005). This suggests that the change in blood pressure following paracetamol is significantly different in children with fever at baseline when compared to children without fever.

5.4.4 Post-hoc analysis of haemodynamic effects of fever removing measurements within 4 hours of paracetamol

The effect of paracetamol on haemodynamic variables was not considered when analysing the effect of fever in 5.4.2 – there was an overlap of cohorts between 5.4.2 and 5.4.3, therefore the effect of paracetamol should be accounted for. Removing data included for the paracetamol analysis, there were data 31 periods of rising temperature up to and above 38°C from 15 patients who did not receive paracetamol during this period. Analysing these using the multi-level regression model as before produced results consistent with those in 3.4.2 – HR and CI increased with temperature, SVI and MBP did not change significantly. Excluding the post-paracetamol data, the change in SVRI with temperature became non-significant (Table 5.11).

	Linear regression coefficient for temperature	2.5 th percentile for temperature coefficient	97.5 th percentile for temperature coefficients
Heart rate	6.77	4.17	9.42
Stroke volume index	0.46	-0.99	1.90
Cardiac index	0.33	0.06	0.60
Systemic vascular resistance index	-50.80	-144.55	40.81
Mean arterial pressure	-0.85	-2.46	0.77

Table 5.11: Coefficients for temperature from multi-level linear regression models for advanced haemodynamic variables excluding data post-paracetamol. Data were included from 31 periods of rising temperature in the fever range from 15 patients. Heart rate and cardiac index were independently associated with temperature using a significance threshold of $p < 0.05$; systemic vascular resistance index, stroke volume index and mean arterial pressure were not associated with temperature changes.

5.5 Discussion

The above analyses aimed to evaluate the effect of temperature and fever on haemodynamic variables in critically ill children, and separately, the impact of the treatment of fever. As paracetamol is the most commonly used anti-pyretic treatment, with well described haemodynamic effects in adults, the haemodynamic effect of paracetamol in critically ill children were evaluated.

5.5.1 Summary of results:

Although haemodynamic variables interact with each other, the following observations can be made based on these data:

- (i) Heart rate: Heart rate correlated positively with temperature, strongly in children fever grade temperature (R^2 0.77). Heart rate increased by 8 beats/min for every 1°C rise in temperature. The effect is not linear – for an increase in temperature between 38 and 39°C, the heart rate increases by 20 beats/min. This result was remarkably well conserved after the adjustment for confounders, in the smaller cohort that underwent cardiac output monitoring – the heart rate increased by 8 beats/min for every 1°C rise in temperature. This was the case when only the rise in temperature to fever grade was considered. In age standardised terms, the z-score for heart rate increased by 0.58 for each 1°C increase in temperature, i.e. an increase by 0.58 standard deviations.

Heart rate did decrease following paracetamol, but the maximum effect was less than 4 beats/min. However, most children did not have a fever when they were given paracetamol. As known from the chapter 3, the mean decrease in temperature following paracetamol in all children is 0.11°C. If only febrile

children were considered, the mean decrease in temperature is 0.78°C following paracetamol: therefore, the expected decrease in heart rate due to a temperature effect alone would be $0.78 \times 8 = 6.4$ beats/min (however this assumes a linear relationship between the effects of paracetamol on temperature and heart rate – so may underestimate the effect). Just over a third of doses of paracetamol in the cardiac output monitored cohort had a fever. The decrease in heart rate by 4 beats/min following paracetamol probably reflects this cohort and the relative effects of paracetamol on temperature, and temperature on heart rate.

- (ii) Stroke volume: There was no correlation between temperature and stroke volume, with the 95% confidence interval of the correlation coefficients crossing 0 for both the continuous temperature cohorts and the fever grade temperature sub-group. Following regression analysis to account for common confounders, there was a 0.66 ml/m² increase in SVI, which although statistically significant, was not clinically significant (baseline mean SVI 27.35, % increase = $0.66/27.35 \times 100 = 2.4\%$). In the fever grade subgroup, the stroke volume was not significantly associated with temperature. SVI did decrease following paracetamol: the effect size was larger than seen with increase in temperature, with a mean decrease of 1.28 ml/m² 2-hours post paracetamol (3.9% decrease from baseline). However, in terms of clinical significance it contributed to less than 5% of the fall in blood pressure seen post paracetamol.
- (iii) Cardiac output: Cardiac output increased with temperature, although the correlation was poor. Following multi-variable analysis, the regression coefficient was just under 0.4. With every 1°C increase in temperature, the cardiac index increased by approximately 10%. Whilst one of the arguments

to treat fever is to reduce tachycardia and improve cardiac filling and output, these data suggest that cardiac output is increased, primarily due to a heart rate increase. Following paracetamol, cardiac index decreased by 0.3 L/min/m², a decrease of 6.7% from baseline. This is likely to be secondary to the decrease in heart rate, given the time-period of change, although the small decrease in stroke volume following paracetamol also contributes.

- (iv) Systemic vascular resistance: Based on multi-variable analysis, systemic vascular resistance *decreased* with temperature. This does not support the hypothesis that peripheral vasoconstriction during fever leads to a rise in systemic vascular resistance. Systemic vascular resistance as estimated from pulse contour analysis did not change post paracetamol – however, the change in blood pressure post paracetamol can only be explained in a small part due to the change in cardiac index and therefore the remaining change can only be explained by a change in vascular resistance.
- (v) Blood pressure: Blood pressure showed little change with temperature. Although the high-resolution monitor data suggested a small increase in systolic and mean blood pressure, and a small decrease in diastolic blood pressure, these changes were too small to be clinically significant. Age-standardised systolic blood pressure increased by a z-score of 0.17 with each 1°C rise in temperature. At fever grade temperatures the increases in blood pressure were more clinically significant, with the mean blood pressure increasing by 6 mmHg with a temperature rise between 39-40°C. Data from the cardiac monitored cohort did not show any change in blood pressure with temperature. Blood pressure did decrease following paracetamol, with the greatest decrease in systolic blood pressure (decrease by 6.7% of baseline 2-hours post paracetamol dose). This is consistent with previous reports,

although the effect is smaller than the 10-15% described in adults. Whilst some of the decrease in blood pressure following paracetamol can be explained by a decrease in cardiac index, the greater effect is possibly due to a change in systemic vascular resistance. There is however considerable uncertainty in making reaching strong conclusions regarding this due to the inherent difficulties in measuring vascular resistance.

5.5.2 Hypothesis testing and Implications of results in critically ill children

The aim of these analyses was to understand the haemodynamic effects of fever in critically ill children. In addition, I sought to demonstrate the effects that paracetamol administration had on haemodynamic variables. In doing so, the following hypotheses were tested:

In critically ill children, heart rate rises by less than 9-10 beats/min for 1°C increase in temperature. Heart rate increases in critically ill children with fever. Overall, the increase in heart rate is by 8 beats/min for 1°C rise in temperature, slightly lower than that described in children presenting to primary or secondary care without shock. However, it is close to previous descriptions from adult ICU. Importantly this change is not linear, as had been described by Tanner. Heart rate increases by up to 15-20 beats/min for a 1°C rise in temperature above 38°C. It is difficult to know whether cytokines that cause fever also contribute to the rise in heart rate, rather than it being the effect of temperature alone. The degree of change is sustained across age groups – evident from the similar relationship between age-standardised heart rate and temperature.

Cardiac output increases with fever. The temperature associated increase in heart rate does not negatively affect the cardiac output: on average cardiac index increases by

approximately 10% for a 1°C rise in temperature. Most of this is secondary to a change in heart rate rather than stroke volume. Although SVI increased with temperature when other confounders were accounted for, this was not so in the febrile cohort. It may be that pyrogenic cytokines have direct effects on stroke volume – it is known, for example, that cold shock is common in children with sepsis [Deep 2016]. The increase in cardiac index is likely to be in response to the increase in metabolic demand needed to mount a febrile response.

Fever does not increase systemic vascular resistance. Based on univariate correlation, there was no consistent change in SVRI following fever. However, following multi-variate analyses, SVRI was shown to decrease with fever. The statistical significance disappeared once measurements taken after paracetamol doses were removed. Measurements post-paracetamol suggest an increase in SVRI following paracetamol doses, even though blood pressure decreased.

The changes in SVRI occur in the opposite direction to the cardiac index. As blood pressure is a product of cardiac index and SVRI, blood pressure remains unchanged. This points to preservation of the baroreceptor response – as the cardiac index increases with temperature and fever, the SVRI adjusts to maintain a static blood pressure. Any temperature related skin vasoconstriction does not affect SVRI, even in children with a high surface area to weight ratio.

Paracetamol is associated with a decrease in blood pressure in critically ill children. Paracetamol was associated with a decrease in blood pressure, typically 2 hours post dose. The size of the effect was small but significant – a 4-6% decrease from baseline. In our cohort of 148 doses, fluid was administered in the 4 hours post paracetamol dose in 33

doses, and vasoconstrictors were increased following 7 doses. Although cardiac index also decreased by a similar magnitude, most of the change in blood pressure was likely to be secondary to changes in SVRI. Measured SVRI changes showed an increase post-paracetamol, although this was not statistically significant. With an intact baroreceptor response, a fall in cardiac output would require a similar increase in SVRI to maintain the blood pressure constant. As the SVRI did not increase significantly post-paracetamol, the blood pressure decreased. It may be possible that paracetamol has direct effects on vascular resistance or affects the baroreceptor reflex.

The blood pressure effect was greater following paracetamol given during fever, although not limited to it. Blood pressure did not increase with temperature. Ergo, the blood pressure effects of paracetamol may be mediated by a fall in SVRI via mechanisms other than the release of vasoconstriction only during fever defervescence. This stands to reason: when not used as an antipyretic, paracetamol is used for analgesia and comfort. Pain is associated with a vaso-constrictive response due to stress – analgesia can relieve this.

Based on the haemodynamic effects observed there is no strong justification to treat fever: although heart rate increases, cardiac index also increases and blood pressure at best does not change. However, treatment may be justified if the metabolic demand of fever is not adequately met by the increase in tissue oxygen delivery, increasing oxygen debt. The most commonly used treatment, paracetamol, decreases both blood pressure and cardiac index.

5.5.3 Limitations

There are several limitations in the analyses, which must be borne in mind when interpreting the data.

- (1) Number of patients in the high-resolution data cohort: Although the greatest strength of using high-resolution data is the number of data-points available for analyses (over 7 million), with repeated measures in the same individual, the number of individual patients was relatively small (n=170). This could bias results, for example if a small group of patients had a particularly strong haemodynamic response to temperature. Most of the patients with continuous measurements were sicker than the overall ICU cohort described in Chapter 2: most of the children underwent unplanned admissions, the median PIM score was higher (4.6 compared to 2.2 in the larger unselected PICU/NICU population described in Chapter 2). The use of multi-level regression analysis aims to minimise this, by accounting for within patient differences, but does not entirely remove it.
- (2) Validation of high-resolution data: While the size of the data-set allows for the detection of a signal amidst noise in the data, this does make it difficult to validate data. Temperature data less than 32°C were considered spurious as this would be considered too low, even in the context of therapeutic hypothermia which is rarely used in PICU/NICU. However other sources of bias may be encountered. For example, a spurious fall in oesophageal temperature can be observed during nasogastric feeding with milk - the temperature probe measures the temperature of the milk. While temperatures less than 32°C were discarded, temperatures lower than the true body temperature, but above 32°C, would not have been. The corresponding heart rate or blood pressure may not have changed, even though the measured temperature dropped. Ideally, rather than choosing a cut-off threshold such as 32°C, data during rapid rises or falls in temperature could have been excluded instead. Seven children had a corrected gestational age of 27 weeks – it would be unlikely for these children to have had core temperature monitoring given the relatively large size of the central temperature probes: these children were probably mislabelled as having core temperature measurements and could have been excluded from the analysis.

- (3) Analysis of non-linear relationships: Historically, the association between temperature and heart rate has been modelled as a linear relationship. Thompson et al suggested a non-linear relationship [Thompson 2011]. From the crude data distribution of high-resolution data in figure 3.3, the relationship between heart rate and temperature does appear to be temperature dependent. Ideally this should therefore be modelled using a non-linear multi-level regression model. However, despite the large number of observations per patient, fitting a non-linear multi-level model on 170 patients would be difficult. In addition, the analysis is complex and would require a higher degree of statistical and computational expertise (although this is work that I intend to take forward in the future). To bypass this problem, coefficients from separate linear models over discrete temperature intervals were used to analyse the differences in the temperature heart rate association. This gave a crude estimate of the non-linear relationship.
- (4) Standardisation of heart rate and blood pressure data: Paediatric heart rate and blood pressure data are age dependent. The age distribution of children admitted to paediatric intensive care units is skewed towards younger children: more than half the children admitted are less than 2 years of age. While absolute values for heart rate and blood pressure may be of use in describing the same population, this may not be the case for adolescent patients. Therefore, crude data were age-standardised and z-scores analysed. Heart rates were age-standardised according the data from Fleming et al. They used several published datasets to calculate the population distribution of heart rates across age groups in healthy children. Critically ill children are likely to have different heart rate distributions: arguably, these should have been used to describe the temperature effects. Normal values for blood pressure are even more problematic. The best available data on normal blood pressure for children come from the NIH Task Force Fourth Report, published in 2004. However, these data are expressed in terms of height centiles. Height data are not routinely collected in our clinical practice, therefore 50th centile height was assumed. This may lead to bias in

most cases, as a lot of paediatric intensive care patients have chronic co-morbidities [O'Brien 2017] and are less likely to fulfil their growth potential. Furthermore, the Fourth Report does not describe normal blood pressure data for infants. The best available infant data are from the NIH Task Force's Second Report, published in 1987. This was used for children under 12 months. Normal blood pressure for infants in the Second Report were greater than 1-3-year olds in the Fourth Report. This lack of congruity may bias differences in response between infants and older children.

- (5) Inaccuracies in pulse contour analysis: Pulse contour analysis is poorly validated in children for cardiac output monitoring. Furthermore, each manufacturer uses proprietary algorithms to estimate stroke volume. Regular calibration using thermodilution is recommended [Proulx 2016]. Thermodilution techniques, including the LiDCO thermodilution device, have been validated in children [Linton 2000], but they remain invasive and were not available for calibration at Great Ormond Street Hospital PICU. Supra-sternal doppler was used for calibration, although not consistently: data pre-calibration were also used assuming that although absolute values would not be accurate, the changes in haemodynamic variables would be. The effect of calibration was minimised by treating calibration episodes separately in multi-variable analysis. Supra-sternal doppler measurement of haemodynamic variables may show inter- and intra-user variability, thereby compounding the error in measurements following calibration. The recommendation of regular calibration with pulse contour analysis is to account from calibration drift. This drift has previously been reported to occur over 2-4 hours, although LiDCO claim their algorithm to be more stable over longer periods of time. Most of the pulse contour analysis data were analysed in consecutive stretches of 2-6 hours, although some longer periods of data were included. Pulse contour analysis also relies on the arterial trace being adequately damped. This is assumed to be the case, although unlikely to consistently be so.

- (6) Lack of central venous pressure data: Of particular note is the inaccuracy in estimating systemic vascular resistance data using pulse contour analysis. SVRI is derived from the difference between mean arterial and central venous pressures (CVP), divided by the cardiac index. CVP is not routinely measured on our PICU due to the poor clinical utility, and the prevalent use of femoral central venous lines. Furthermore, the LiDCORapid analyser does not allow direct continuous input of the CVP, but rather uses CVP as a static variable (albeit one that can be changed). In all LiDCO measurements used, a CVP of 7 mmHg was assumed as a default. This introduces an error in SVRI measurements: if the CVP increased to 15, then in a child with a CI of 4 L/min/m², the SVRI would overread by 160 dynes/cm⁵/m². The change in SVRI described per 1°C rise in temperature is similar to this, and therefore must be treated with caution.
- (7) Overlap between temperature related haemodynamic data and paracetamol related haemodynamic data: Haemodynamic data from the same recordings were used for temperature haemodynamic relationships and paracetamol haemodynamic relationships. For the former, the haemodynamic effects of paracetamol were not accounted for. This could confound the results, even though the relationships were distinct: there was positive association between temperature and HR and temperature and CI; there was negative association between temperature and SVRI. In contrast, paracetamol was associated with a fall in HR, SVI, CI, and MBP. Post hoc, data from the time points included in the paracetamol analysis were excluded: the associations between fever and haemodynamic variables were preserved, apart from for SVRI.
- (8) Retrospective data collection for confounders: Pulse contour analysis data were analysed in patients who had pulse contour analysis due to clinical reasons. This is a strength: pulse contour analysis was clinically used in children who had suspected haemodynamic instability. The haemodynamic effect of fever and paracetamol is most important in these children. Confounder data however were collected retrospectively from the electronic health record. This introduced bias in the timings, and potential

inaccuracies in data recorded. For example, if vasoconstrictor dose was increased, this may not be charted contemporaneously, but the increased dose may be charted in the following hour. Ideally however, it would have been useful to have measured changes in oxygen delivery prospectively, alongside the measurement of oxygen consumption.

- (9) Discordant timing between haemodynamic and confounder data: Electronic health record data are typically charted hourly. Haemodynamic data were recorded at much higher frequencies. The haemodynamic data had to be summarised into hourly values, leading to loss of data. In order to do so, the mean of 200 measurements around the hour mark were used. However, due to the compression algorithm used by LiDCOrapid in recording haemodynamic data, the frequency of data recording was variable – higher resolution data were available for shorter recordings. Therefore 200 measurements represented different time periods: 200 measurements recorded at 3 second frequencies represent 10 minutes, but at 6 second frequency represent 20 minutes. The variability in data may be greater in lower frequency data.
- (10) Categorical confounder data: Given the relatively small number of patients and large numbers of patients, confounder data were categorised to represent change e.g. in drug doses administered. This is particularly problematic for vaso-active inotropic drugs as many of the haemodynamic effects may be dose dependent. For example, adrenaline is thought to be a vasodilator at low doses, but a potent vasoconstrictor at high doses. Furthermore, the doses of vaso-active inotropic drugs were combined to produce a vaso-active inotrope score (VIS) and the change in this was categorised. Given that this score includes both vasoconstrictors such as noradrenaline and vasopressin, and vasodilators such as milrinone, the change in VIS is unlikely to have a uniform effect. Also, the haemodynamic changes associated with the confounders may have different time periods: vaso-active inotrope drugs may have a quick onset and offset, but changes in sedation may take peak effect over minutes or hours.

- (11) Inclusion of intravenous and enteral paracetamol doses: Haemodynamic data following both intravenous and enteral doses of paracetamol were included. The time course of haemodynamic changes is likely to be different according to route of administration. Also, the serum levels of paracetamol may be different according to administration route: serum paracetamol levels were not measured. Although all doses were between 10-15mg/kg, the dose effect of paracetamol on haemodynamic variables were not measured.
- (12) External cooling data: Data were not available for the use of external cooling such as the use of fans or ice. Cooling mattresses were used on 9 patients, and these data were included. However, the haemodynamic effects of paracetamol, or temperature, may be affected by the use of external cooling (more likely to lead to peripheral vasoconstriction). Care was taken to exclude measurements when there was a documented change in cooling temperature, for example during re-warming. Similarly, 2 children were receiving continuous veno-venous haemofiltration. This may have had a unique effect on their haemodynamic parameters, which was not accounted for. Care was taken however to not include children who were being initiated on continuous veno-venous haemofiltration, as the haemodynamic variables would be most unstable during this period.

5.6 Conclusions

The objective of this chapter was to evaluate the haemodynamic effect of fever and its treatment on critically ill children admitted to PICU. These data confirm that heart rate increases with fever. Once confounders within PICU are accounted for, heart rate increases by approximately 8 beats/min for each 1°C increase in temperature, although a 15-20 beats/min increase in heart rate can be observed with a 1°C rise in temperature in the fever range. Cardiac output is not compromised, and on average increases with temperature. This is secondary to the rise in heart rate rather than an increase in stroke volume. Systemic vascular resistance does not significantly increase with fever. Paracetamol causes a

decrease in blood pressure 2-hours post paracetamol dose. While some of this decrease is related to a small decrease in cardiac output, most of this effect is related to changes in systemic vascular resistance. This effect is not limited to doses used during fever i.e. the effect is not necessarily temperature related.

Based on these data, there is no good haemodynamic reason to treat fever – indeed using paracetamol to treat fever may be detrimental by reducing organ perfusion pressure and tissue oxygen delivery. Cardiac output, therefore, oxygen delivery, increases with fever. This is likely in response to the increase in oxygen consumption associated with fever. If both increases in oxygen consumption and delivery are in proportion to each other, then fever is unlikely to lead to an oxygen debt or have a detrimental effect on patient outcomes due to this. In the next chapter, I explore the impact of fever on ICU outcomes in children.

Chapter 6: The effect of fever on critical illness outcomes

6.1 Introduction

So far, I have provided evidence that fever is common in children admitted to PICU, is associated with an increase in heart rate, and in some children an increase in cardiac output. On average, the increase in cardiac output was estimated to be just under 10% per °C rise in temperature. Based on adult data, fever is associated with an increase oxygen consumption by 10-12.5% per °C rise in temperature [Altschule 1945, Manthous 1995]: although the data from Chapter 4 was insufficient to draw any firm conclusions, they remain consistent with this. Paracetamol is used commonly, with and without fever. Not every episode of fever is treated with paracetamol. The temperature effect of paracetamol is modest, with temperature falling by 0.78°C if used in febrile children.

It is therefore likely that fever is **not** associated with a significant imbalance in oxygen consumption and delivery, and therefore an oxygen debt. Treating fever may reduce oxygen consumption, although most of the energy consumption may have occurred to generate the fever before treatment. Given an oxygen debt is unlikely, at least in most patients, treating fever to reduce an oxygen debt is a weak argument.

If not beneficial, is there a harm in treating fever? Paracetamol may come at a cost, reducing blood pressure, albeit to a small degree. What remains unknown is how fever is associated with outcomes in critically ill children. As fever is unlikely to cause an oxygen debt in most cases, this effect of fever on critical illness outcomes may be low. On the other hand, laboratory experiments point to an immune benefit, which may be reflected in improved outcomes in children with infection who have a fever.

Young's observational study of over 600000 critically ill adult patients provided the most robust association between early fever and survival in patients admitted with infection to ICU

[Young 2011]. This evidence from Australia, New Zealand and the UK raises an interesting question – is the optimal temperature in critical illness universal? Patients with a peak temperature between 39.0-39.4°C in the first 24 hours of admission had the lowest risk of mortality in Australia and New Zealand; in the UK the lowest risk was in those with a temperature between 38.0-38.4°C. It is tempting to think that atmospheric temperature could have a role to play: the higher atmospheric temperatures in Australia, may allow a greater rise in body temperature without the need for increased energy expenditure. One could hypothesise this allows the higher body temperature to have beneficial immune effects without the detrimental effects of using scarce energy resources.

While tempting, it may be too weak to argue based on Young et al's results alone. The study did not capture any data on interventions – it is possible that fever was more aggressively treated in the UK compared to Australia and New Zealand. Environmental temperature regulation is likely to be similar within the ICU in the UK, Australia and New Zealand, as are other ICU interventions which will impact on body temperature, such as the set temperature for ventilator humidification or the temperature of intravenous fluids.

In order to test this hypothesis further it may be better to compare two populations in distinct climate zones, with one cohort not subject to the ICU measures of temperature control, including air conditioning and control of fluid and gas temperatures. This will be difficult to construct, as most ICU environments are subject to similar controls. I will therefore attempt to test this using a UK PICU cohort, and a cohort of children enrolled to the FEAST (Fluid as Expansive Supportive Therapy trial) based in Kenya, Uganda and Tanzania [Maitland 2011]. These children had life threatening infections but did not have intensive care resources available to them. Whilst the latter will affect mortality, the aim will be to test whether the optimal temperature for outcome is different in the two cohorts. The FEAST population may have a higher or lower optimal temperature: a higher temperature if the immune benefit is the major determinant of the outcome, a lower temperature if cellular energy availability is more critical.

Furthermore, the aim of FEAST was to test the effect of fluid boluses on mortality at 48 hours in these children with severe infection. Fluid boluses are given with the aim to improve oxygen delivery. The trial concluded that despite this intended effect, mortality was higher in children who received fluid boluses when compared to those who did not (this could be because of the intended effect: a sudden increase in oxygen delivery for example could be harmful). If fever did cause an oxygen debt in these children, who were critically unwell without intensive care support, and increased the risk of mortality, it would be expected that fluid may have a different effect on children with fever and those without. This was seen in the more recent TRACT trial [Maitland 2019] where two volumes of blood transfusion were compared in children with severe anaemia (although the cause of anaemia was not reported, over 60% of the studied cohort had malaria and just under a third had sickle cell disease; children with chronic liver, kidney or heart disease and children with malignancies were excluded). The secondary analysis of the trial data showed a clear distinction in effects of volume of blood transfused according to temperature at randomisation. Those who had a temperature $<37.5^{\circ}\text{C}$ benefited from a blood transfusion volume of 30ml/kg of whole blood. Those who had a temperature $\geq 37.5^{\circ}\text{C}$ on the other hand benefited from a blood transfusion volume of 20ml/kg. Based on the argument that fever increases oxygen debt, these results are difficult to explain: children with fever should have benefited more with a greater increase in oxygen delivery, theoretically provided by the greater volume of blood transfusion (both the higher volume, leading to an increase in cardiac output, and the rise in haemoglobin concentration should have increased oxygen delivery).

However, based on the TRACT results alone it is not possible to completely refute the argument that oxygen debt is greater in fever for the following reasons: (a) these children were not critically ill but had severe anaemia which may have been chronic – oxygen debt therefore may have been better tolerated and may not have contributed to mortality. Instead, the increase in oxygen delivery may have led to an increase in reactive oxygen species in those chronically adapted to anaemia; (b) whole blood was used in many cases, which could

have led to an immune reaction, especially in children with fever; (c) although the haemoglobin concentration was higher in those who received the larger blood volume, the volume alone may not have been well tolerated in children with fever. This last effect, the effect of volume in children with fever on mortality, can be tested in the FEAST cohort retrospectively.

In this chapter, I will use the retrospective observational data from Chapter 2 to explore the association between early temperature and outcomes in PICU. I will also explore if the association is translatable to FEAST cohort to try and uncover the impact that intensive care may have on the effect of temperature. Finally, I will explore whether there was an effect of temperature at randomisation on the primary outcome of mortality at 48 hours in children randomised to the FEAST trial.

6.2 Aims and hypothesis

Aims of the study:

- (i) To describe the association between maximum temperature in the first 24 hours of PICU admission and PICU mortality.
- (ii) To describe the same association in a cohort of sub-Saharan African children with severe infections but without the provision of intensive care, to compare with the UK PICU cohort.
- (iii) To explore the effect of fever on mortality at 48-hours in children recruited to the FEAST trial according to the interventions they received.

Null hypotheses:

The UK PICU cohort demonstrates no association between mortality and the maximum temperature in the first 24 hours of PICU admission.

The sub-Saharan African cohort show no association between mortality and maximum temperature in the first 24 hours post presentation to healthcare services.

Fever at randomisation had no effect on the outcome according to interventions in the FEAST trial.

Alternative hypotheses:

The UK PICU cohort demonstrates a U-shaped association between maximum temperature in the first 24 hours of admission and PICU mortality, with fever (temperature $\geq 38.0^{\circ}\text{C}$) providing a survival advantage relative to a temperature of 36.5°C .

The sub-Saharan African children show a different optimal temperature for survival to the UK PICU cohort.

In the FEAST trial, fever at randomisation favoured fluid administration compared to the arm that received no fluid.

6.3 Methods

6.3.1 Analysis of relative effects of maximum temperature in first 24 hours on mortality in two populations of critically ill children

Study design and setting: This was a retrospective observational study of two separate cohorts – a GOSH PICU cohort from Great Ormond Street Hospital (GOSH) and a cohort of sub-Saharan with infection enrolled into the Fluid as Expansive Supportive Therapy (FEAST) trial.

Populations:

- a) GOSH PICU cohort: Data from all children admitted to the general paediatric intensive care units (PICU), neonatal intensive care unit (NICU) and cardiac intensive care unit (CICU) at Great Ormond Street Hospital between 1st April 2012 and 31st

December 2017 (68 months) were included (same cohort as in Chapter 2). Admissions were identified from data submitted to the Paediatric Intensive Care Audit Network (PICANET), including admission and discharge dates and times. As the general PICU and NICU was considered together by PICANET and managed by the same medical team, data were considered together for P/NICU.

- b) FEAST cohort: Data from all children enrolled in the FEAST trial were included. Children were enrolled from 6 centres in Kenya, Tanzania and Uganda between 2009-2011. The study was designed to compare the effect of saline, albumin or no fluid bolus in the early resuscitation of children with severe infection. Children were included if they (i) were between 60 days and 12 year of age, (ii) presented with a severe febrile illness, (iii) complicated by impaired consciousness and/or respiratory distress, and with impaired perfusion (capillary refill time ≥ 3 seconds, lower limb temperature gradient, weak radial pulse, or severe tachycardia). Children were excluded if they (i) were severely malnourished, (ii) had acute gastroenteritis, (ii) had non-infectious causes of shock such as trauma, surgery or burns, or (iv) had a condition for which volume expansion was contra-indicated. Children enrolled were randomised to receiving wither no fluid bolus, 0.9% sodium chloride (20-60ml) or 4.5% human albumin solution (20-60ml). The children were treated on general paediatric wards in the absence of intensive care provision. Children were treated with intravenous fluids, antibiotics, anti-malarial drugs, anti-pyretics and anti-convulsant drugs as needed.

Variables and data sources:

- a) GOSH PICU cohort: Temperature data were collected as described in Chapter 2. Data regarding survival at PICU discharge were available from data submitted to PICANET. In addition, the Paediatric Index of Mortality (PIM) score, and the type of

admission, emergency or elective, were also obtained from data submitted to PICANET from the Clinical Information Team at GOSH.

- b) FEAST cohort: Data were requested from the FEAST trial team for analysis of the association between temperature and mortality through an application to the trial steering committee. Data were provided for admission date, temperature, survival and data to calculate the FEAST Paediatric Emergency Triage (PET) score and the PIM score [George 2015]. The PET score was derived from the FEAST dataset to predict mortality and validated using an independent data set. The score uses 8 clinical variables – temperature, heart rate, capillary refill time, conscious level, pallor, respiratory distress, lung crepitations and volume of radial pulse, producing a score of 0-10. Only data for base excess, systolic blood pressure and pupil reaction were available for the PIM score. Data for most of the other variables however were derivable from the inclusion and exclusion criteria i.e. all emergency admissions, none post theatre or cardio-pulmonary bypass, no low risk or high-risk diagnoses. Data on PaO₂/FiO₂ were not available due to no arterial blood gas sampling: as per PIM, all children were assigned a value of 0 for this.

Bias: The temperature distributions over time were different between units, planned and unplanned admissions and infants and older children, as demonstrated in Chapter 2. Bias could be introduced by including different sub-groups together. While the whole cohort was analysed to understand the association between temperature and mortality in a representative mixed ICU population, sub-group analysis was also carried out to explore differences. This was particularly important given the hypothesised differences in the temperature and mortality relationship in those with infection and those without.

Study size: a sample size calculation was not undertaken for the GOSH cohort – all data available from the electronic health record system were used until the time of data analysis. The FEAST study was conducted to detect a relative mortality reduction of 33% in the saline

arm and 40% in the albumin arm with 80% power and a two-sided alpha level of 0.05. This required a sample size of 3600 children with assuming a mortality level of 11%.

Data analysis:

The maximum temperature in the first 24 hours of admission (Tmax) was used to test associations with mortality. This was calculated according to hours from admission rather than calendar days. Continuous variables Tmax and PIM based risk of mortality were tested for normality using the Kolmogorov-Smirnov test. Normal data were defined using mean and standard deviation; non-normal data as median and inter-quartile ranges (IQR). Univariate comparisons were made using the Student's t-test for normal data and the Mann-Whitney test for non-normal data.

Although adult data suggest a U-shaped curve with increased risk of mortality with high and low Tmax, this has not been described in children. Therefore, the first step was to assume a proportional effect (either high Tmax or low Tmax associated with higher mortality). The univariable association between death and Tmax was described using receiver operator characteristic (ROC) curve statistics. The area under the ROC curve was used as summary statistic, with 95% confidence intervals (CI). Where suitable, the area under ROC curves were compared using DeLong's method.

To account for the severity of illness, the risk of mortality excluding any temperature variables was used. For the GOSH PICU cohort the PIM based risk of mortality was used. As the PET score includes temperature as a variable, a modified PET score (mPET) was used by removing the temperature component, thereby giving a score out of a maximum possible of 9. The calculated PIM for FEAST patients and the mPET scores were compared using ROC curves and the best predictor was used in the multi-variable analysis for Tmax and death.

To assess the nature of the relationship between Tmax and mortality in more detail, multi-variable analysis was undertaken. Tmax was divided into categories of 0.5°C and used in a

logistic regression equation with the risk of mortality – replicating the analysis of Young et al [Young 2012]. However, as Tmax is a continuous variable with an unlikely linear relationship with risk of mortality, a restricted cubic spline transformation of the Tmax data, followed by logistic regression was used to define the association between Tmax and death. The knots were a priori chosen at the 10th, 50th and 90th centile for Tmax. The adjusted odds ratio of death for a continuous range of Tmax was expressed relative to a Tmax of 36.5°C.

Young et al showed a difference between the association between temperature and death according to whether they were admitted with an infection or not. Data regarding diagnosis at admission were not available therefore this could not be replicated in the GOSH PICU cohort (the FEAST cohort only included children with infection). However, as a surrogate marker of infection, the UK cohort were divided into planned and unplanned admission, with the assumption that infection was more likely in children with unplanned admission – the national Fever Observational study showed that nearly 60% of children with unplanned admission had a proven or suspected infection [Peters 2018]. The GOSH cohort were also analysed according to the unit of admission (general PICU and NICU, or CICU), and according to age (<1 year and 1 year and older).

Patient consent: For the GOSH cohort, Individual patient consent was not sought as this was a case report study involving routinely collected data, with no reporting of patient identifiable data. For the FEAST cohort, individual consent was sought for data use at the time of randomisation. Permission to use the data was granted through an application to the Trial Steering Committee.

6.3.2 Analysis of the effect of fever on FEAST trial outcomes

Study design and setting: This is a post hoc analysis of the FEAST randomised controlled trial results according to presence or absence of fever at randomisation of children to either

receive fluids (0.9% sodium chloride and 4.5% human albumin solution arms combined) or no fluids.

Population and Data Collection: Children recruited to the FEAST trial, as described in Section 5.3.1. The data provided for association between temperature and mortality were used.

Data analysis: The primary outcome measure in the FEAST trial was mortality at 48 hours from randomisation. As the outcomes were no different between those who received 0.9% sodium chloride and 4.5% human albumin solutions, and both fluids are given to improve cardiac output and hence oxygen delivery, these arms were combined into those who received fluid for this analysis. Also, there were two strata of randomisation for the fluid arms in FEAST according the volume of fluid used (20 or 40ml/kg initially): both strata were grouped within the fluid arm.

In keeping with the rest of this thesis, fever was defined as a temperature of $\geq 38^{\circ}\text{C}$ rather than 37.5°C as used in the TRACT trial. All temperatures were measured from the axilla – the type of thermometer used (digital/analogue) was not specified. Children were categorised into those with no fever and those with fever at randomisation. Temperature at randomisation was chosen in case the intervention itself changed the likelihood of developing fever (e.g. if children were unable to generate a fever because of inadequate oxygen delivery to tissues then a fluid bolus could increase oxygen delivery and facilitate a fever subsequently).

Odds ratios for 48-hour mortality following fluid resuscitation in children with and without fever at randomisation were calculated. The odds ratios could be compared and considered to be significantly different if the 95% confidence intervals did not overlap. Although the arms were randomised and therefore balanced for those receiving fluid and those not, this balance may not have been maintained in those with fever and those without. Therefore, the bedside modified PET score, without the temperature variable, was used in a logistic regression

model to estimate the adjusted odds ratios. The I^2 statistic for heterogeneity was calculated according to Neyeloff et al [Neyeloff 2012] using a random effects model.

In addition, a separate model was analysed using fluid allocation and fever as interacting variables – the interaction term was tested for statistical significance.

All data were analysed using Microsoft Excel (Microsoft Corp. WA, USA) and R (www.cran.r-project.org). All SQL, visual basic and R code used are detailed in Appendix D.

6.4 Results

6.4.1 Association between Tmax and death in a UK PICU

6.4.1.1 Association between Tmax and death in the whole GOSH ICU cohort

There were 10379 admissions over the 68 months between 1st April 2012 and 31st December 2017. Temperature data were available for 10125/10379 (97.6%) for the first 24 hours of admission. Of the 10125 children who had temperature data available, 9663 survived to ICU discharge and 462 died (mortality rate 4.6%). There were 5425 (53.6%) children admitted to general PICU or NICU, and 4700 admitted to CICU; 4694 (46.3%) admissions were unplanned and 5431 planned; 5565 (55.0%) children were less than 1 year of age and 4560 were 1 year or older.

The distribution of Tmax was not normally distributed (Kolmogorov-Smirnov D-statistic 0.11, p -value $< 2.2 \times 10^{-16}$). The median Tmax was 37.7°C, (inter-quartile range 37.4-38.1°C). The distribution of Tmax according to survivors and non-survivors is shown in Figure 6.1. There was a statistically significant difference between Tmax in survivors (median 37.7°C, IQR 37.4-38.1°C) and non-survivors (median 37.6°C, IQR 37.1-38.1°C) following the Mann-Whitney-Wilcoxon test.

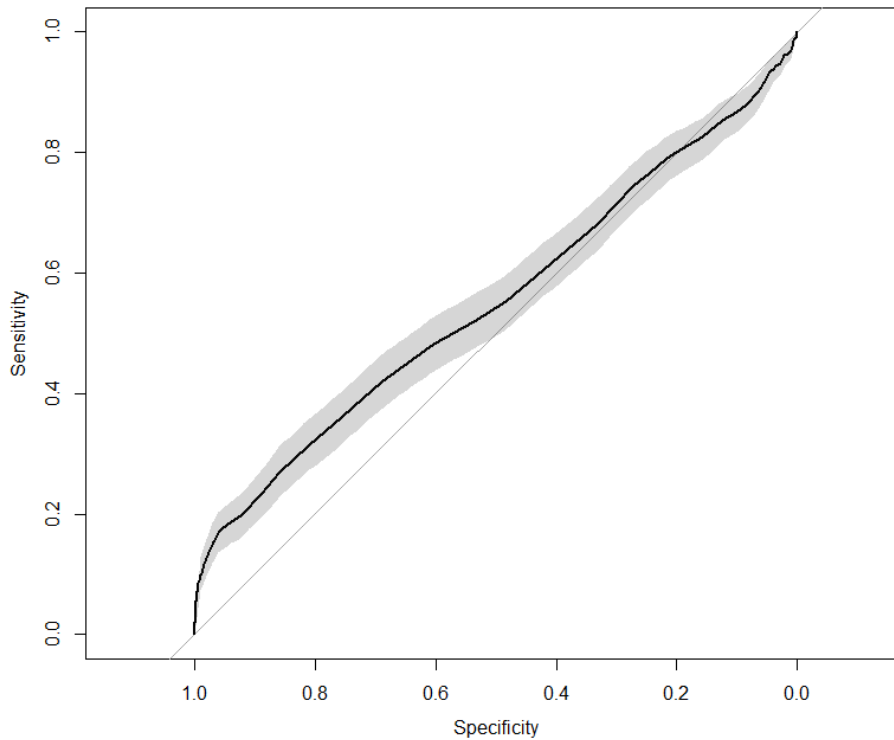


Figure 6.1: Distribution of maximum temperature in the first 24 hours according to survivors and non-survivors in the GOSH cohort. The distribution of Tmax is shown for 9663 survivors (continuous line) and 462 non-survivors (dashed line) admitted to ICU at Great Ormond Street Hospital over a 68-month period. There is a significant difference in the distributions following the Mann-Whitney test ($W=2.5 \times 10^6$, $p\text{-value}=9.5 \times 10^{-5}$).

Tmax however is a poor predictor of mortality in the GOSH PICU cohort – the area under the ROC curve is 0.55 (95% CI 0.52-0.59) (Figure 6.2). This suggests that there is no proportional relationship in any direction i.e. an increase or decrease in Tmax is not associated with a proportional increase in mortality.

However, Tmax could have a more complex relationship with mortality, as described by Young et al in adult ICU patients. To replicate the analysis used by Young et al [Young et al 2012] Tmax was categorised into 0.5°C intervals. The categories were used in a log regression model along with PIM to adjust for severity of illness. The highest odds of death

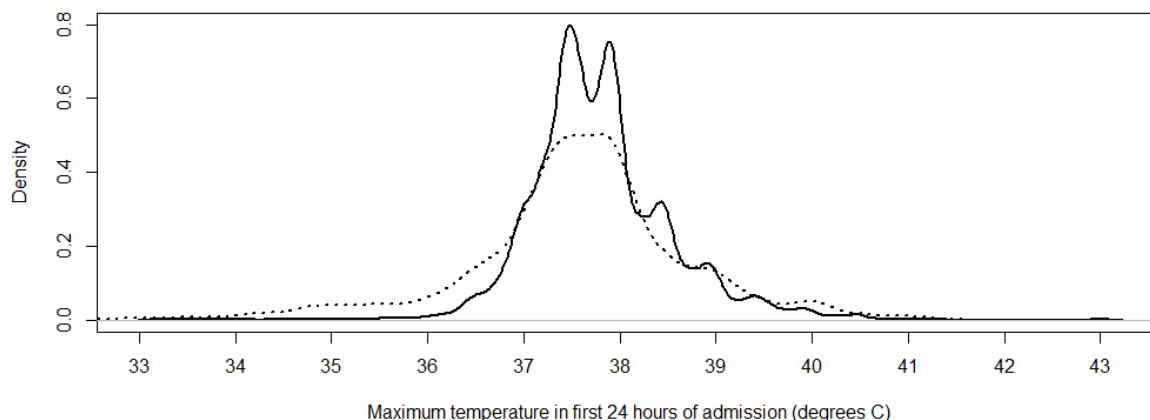


Figure 6.2: Receiver operator characteristic curve for maximum temperature in the first 24 hours after admission to ICU (n=10125). The shaded grey area represents the 95% confidence interval. The area under the curve 0.55 (95% CI 0.52-0.59).

occurred at low temperatures, with the odds rising again above a Tmax of 38.9°C. The lowest odds ratio of death was at 37.4-37.9°C (Figure 6.3).

However, as temperature is a continuous variable, which is known to have a non-linear relationship with mortality, restricted cubic splines were used to transform Tmax with 3 knots at the 10th, 50th and 90th centiles (corresponding to 37.0, 37.7 and 38.7°C). The spline transformed Tmax was then used in a logistic regression model with PIM to adjust for the severity of illness at admission. The PIM adjusted odds ratios for Tmax, relative to a 36.5°C is shown in Figure 6.4. The odds ratio of death is highest at low temperatures, but also increases as Tmax increases above 38°C. However, relative to 36.5°C, the odds ratio of death remains significantly lower until the Tmax is nearly above 39°C. The Tmax associated with the lowest odds ratio of death is 37.6°C.

6.4.1.2 Analysis of the GOSH ICU cohort according to sub-groups

Planned versus unplanned admissions: The distributions of Tmax for unplanned and planned admission are shown in Figure 6.5. The median Tmax for unplanned admissions

was 37.8°C (IQR 37.4-38.3°C); for planned admissions the median was 37.7°C (IQR 37.4-38.0°C). The two sub-groups are significantly different (Mann-Whitney test $W=1.12 \times 10^7$, p -value= 3.5×10^{-13}), with higher temperatures in the unplanned admissions. The mortality rate was 387/4694 (8.2%) in unplanned admissions and 76/5431 (1.4%) in planned admissions. For unplanned admissions there was a difference in Tmax between survivors and non-survivors, with non-survivors significantly colder (non-survivors median Tmax 37.6°C, IQR 37.1-38.2°C; survivors median Tmax 37.8°C, IQR 37.4-38.3°C, p -value 2×10^{-6}) (Figure 6.6). There was no difference between Tmax in survivors and non-survivors in planned admissions (non-survivors median Tmax 37.6°C, IQR 37.2-37.9°C; survivors median Tmax 37.7°C, IQR 37.4-38.0°C, p -value 0.11).

Logistic regression was applied to restricted cubic spline transformed Tmax data to evaluate the optimal Tmax for planned and unplanned admissions. The lowest odds ratio for death was at a Tmax of 38°C for unplanned admissions, while it was at a Tmax of 37.3°C for planned admissions (Figure 6.7).

General PICU/NICU versus CICU: The Tmax was significantly lower for children admitted to CICU (median 37.6°C, IQR 37.3-38.0°C) compared to general PICU/NICU (median 37.8°C, IQR 37.4-38.3°C; p -value 2.2×10^{-16}) (Figure 6.8). Tmax was lower in non-survivors in both units (Figure 6.9), more evidently so in CICU. The adjusted odds ratios of death show a similar association with temperature between units, with the lowest odds ratio of death between 37.8°C in CICU and 37.4°C for general PICU/NICU (Figure 6.10).

Children less than 1 year and those 1 year and over: Children <1 year of age had a significantly lower Tmax compared to those 1 year and over (children <1 year median Tmax 37.6°C, IQR 37.3-38.0°C, children 1 year and over median Tmax 37.9°C, IQR 37.4-38.4°C, p -value $<2.2 \times 10^{-16}$) (Figure 6.11). Non-survivors had lower Tmax in both sub-groups (Figure 6.12). The odds ratios of death were lowest at 37.6°C in children <1 year and 37.7°C in children 1 year and over. The odds ratio of death climbed steeply as Tmax was below 36.5°C in children 1 year or over (Figure 6.13).

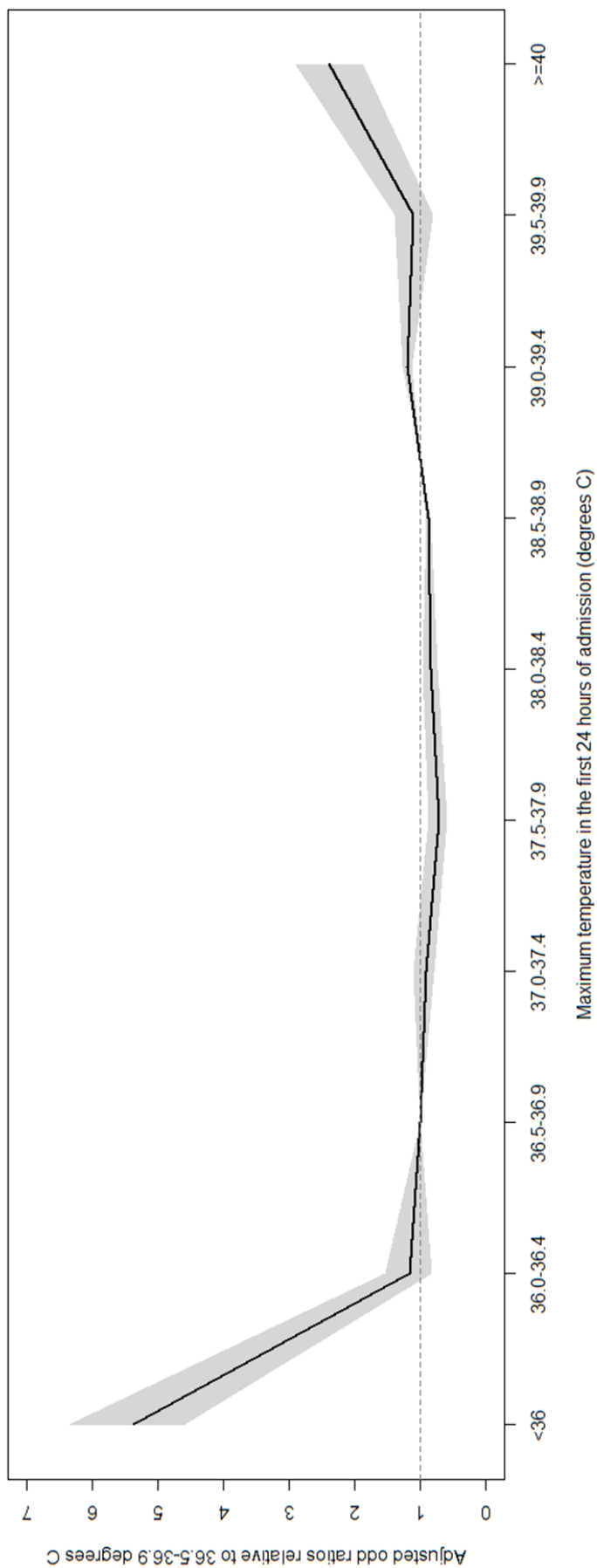


Figure 6.3: Adjusted odds ratios for ICU mortality according to the maximum temperature in the first 24 hours categorised into 0.5°C intervals. The odds ratios are relative to the odds ratio for a maximum temperature of 36.5-36.9°C and are adjusted for the PIM score at admission. The shaded area represents the 95% confidence intervals for the adjusted odds ratios.

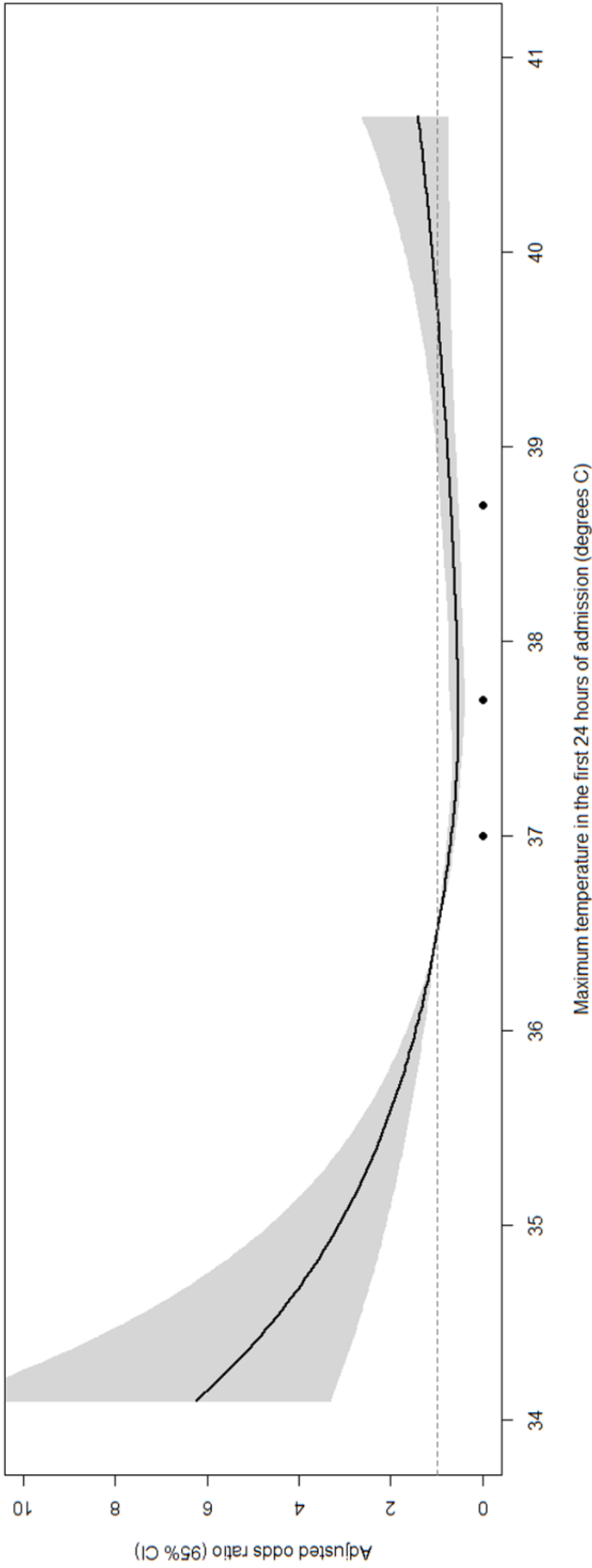


Figure 6.4: Adjusted odds ratios for ICU mortality according to the maximum temperature in the first 24 hours, relative to the odds ratio for a maximum temperature of 36.5°C. Temperature was transformed using 3-knot restricted cubic splines. The black dots represent the 3 knots at 37.0, 37.7 and 38.7°C (corresponding to the 10th, 50th and 90th centiles for the cohort). The odds ratios are adjusted for the PIM score at admission. The shaded area represents the 95% confidence intervals for the adjusted odds ratios.

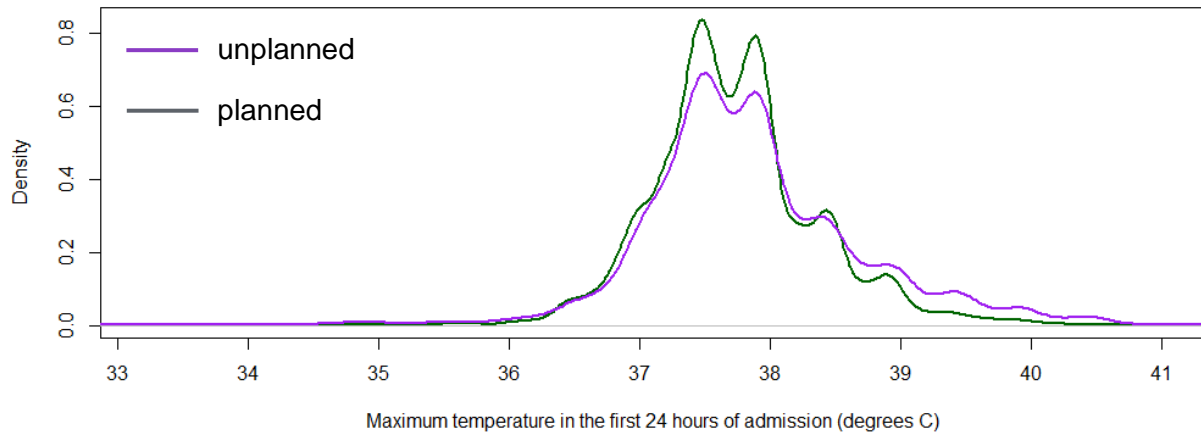


Figure 6.5: Distribution of maximum temperature in the first 24 hours according to type of admission. Data are shown for 4694 unplanned (purple) and 5431 planned (green) admissions. There is a significant difference in the distributions following the Mann-Whitney test ($W=1.12 \times 10^7$, $p\text{-value}=3.5 \times 10^{-13}$).

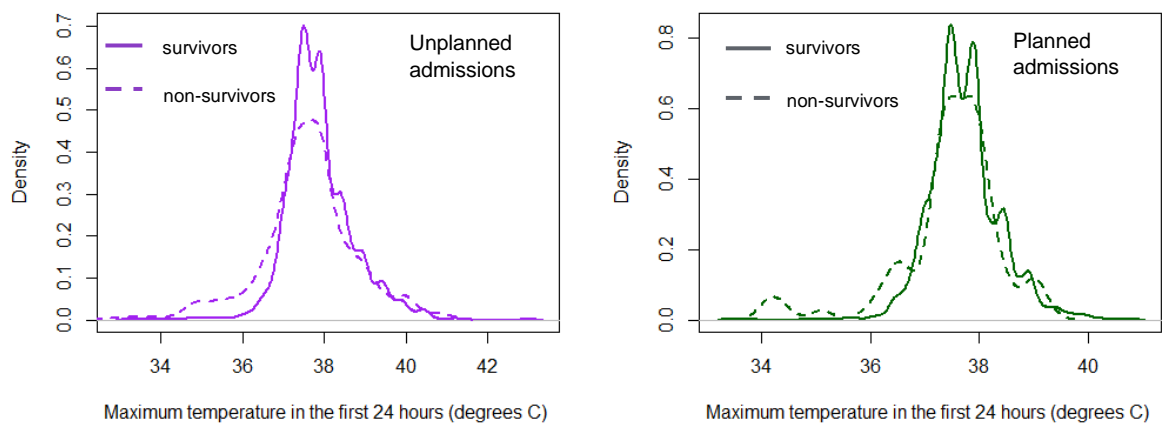


Figure 6.6: Distribution of maximum temperature in the first 24 hours according to type of admission. Data shown for survivors (continuous line) and non-survivors (dashed line) in (a) unplanned admissions (left, purple) and (b) planned admissions (right, green). There were 4308 survivors and 387 non-survivors amongst unplanned admissions and 5355 survivors and 76 non-survivors amongst planned admissions. There is a significant difference between the maximum temperatures of survivors and non-survivors for unplanned admissions ($p\text{-value}=2.44 \times 10^{-6}$) but not for planned admissions ($p\text{-value}=0.11$) following the Mann-Whitney test.

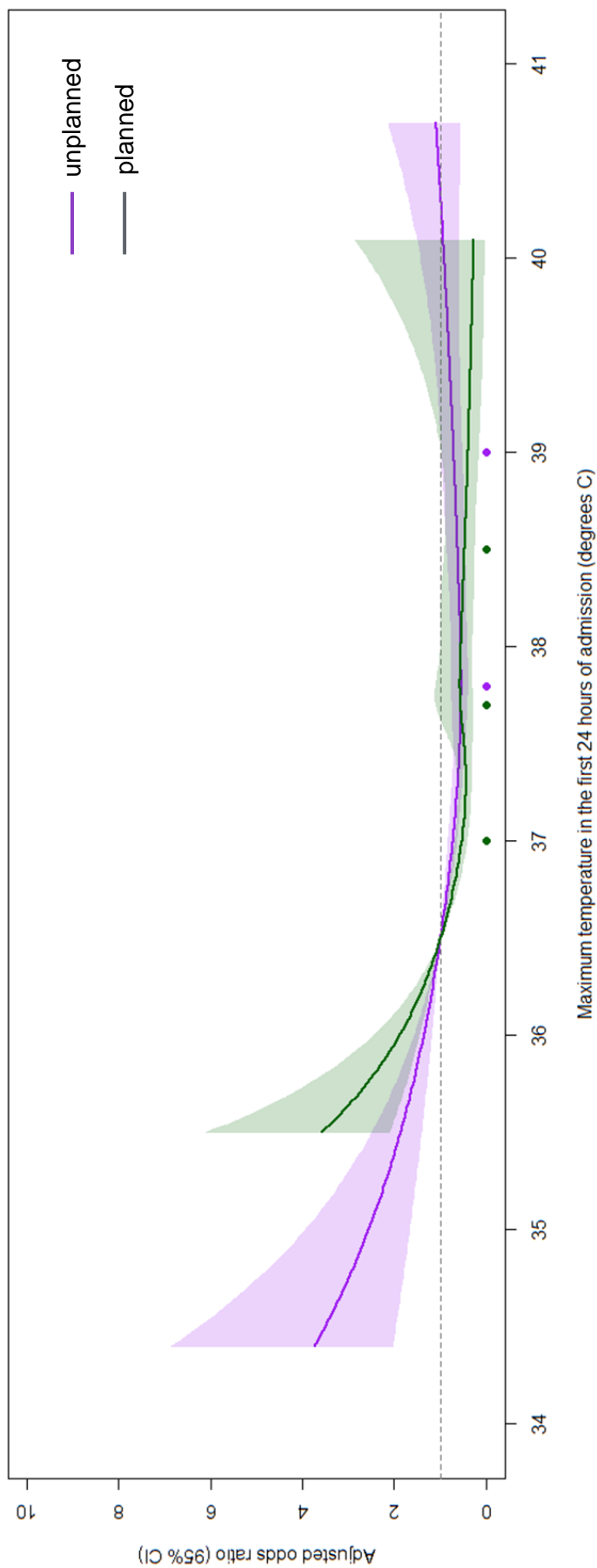


Figure 6.7: Adjusted odds ratio of death according to maximum temperature in the first 24 hours of admission for different types of admission. The purple line shows the odds ratios following unplanned admission and the green line following planned admission. All odds ratios were calculated relative to the odds ratio when the maximum temperature is 36.5°C and adjusted for severity of illness using the PIM score. Odds ratios were calculated using restricted cubic splines (3 knots, 4 degrees of freedom). Knots were a priori assigned to the 10th, 50th and 90th centiles of the maximum temperatures in the cohort – this corresponded to 37.0, 37.8 and 39.0°C in the unplanned admission cohort and 37.0, 37.7 and 38.5 in the planned admission cohort.

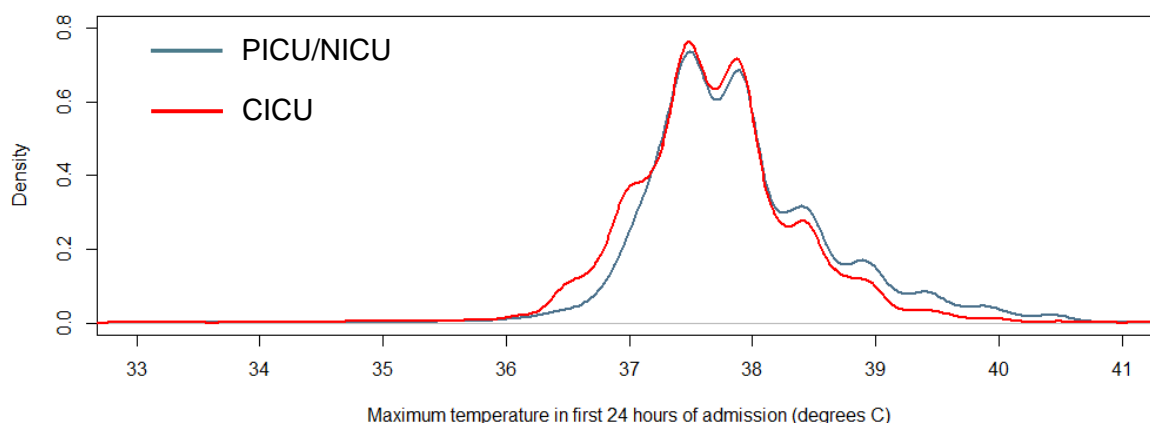


Figure 6.8: Distribution of maximum temperature in the first 24 hours according to unit of admission. Data are shown for 5425 PICU/NICU (blue) and 4700 CICU (red) admissions. The distribution for general PICU/NICU had a median Tmax of 37.8°C, IQR 37.4-38.3°C, CICU a median of 37.6°C, IQR 37.3-38.0°C. There is a significant difference in the distributions following the Mann-Whitney test, with the median Tmax slightly higher of PICU/NICU (median difference 0.2°C, $W=1.45 \times 10^7$, $p\text{-value}=2.2 \times 10^{-16}$).

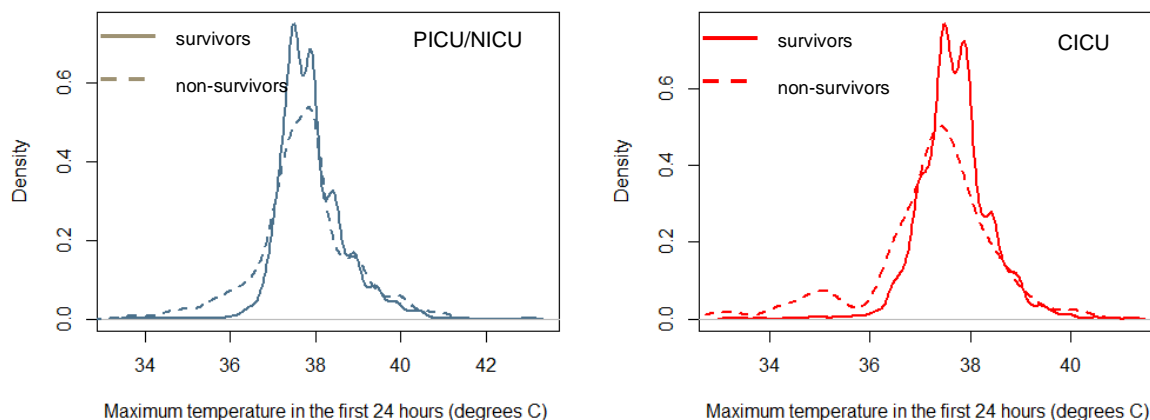


Figure 6.9: Distribution of maximum temperature in the first 24 hours according to survival to discharge and unit of admission. Data shown for survivors (continuous line) and non-survivors (dashed line) in (a) PICU/NICU (left, blue) and (b) CICU (right, red). There were 5256 survivors and 346 non-survivors in PICU/NICU and 4637 survivors and 140 non-survivors in CICU. There is a significant difference between the maximum temperatures of survivors and non-survivors, with Tmax being lower in non-survivors in both PICU/NICU admissions ($p\text{-value}=0.005$) and in CICU admissions ($p\text{-value}=5.85 \times 10^{-6}$) following the Mann-Whitney test.

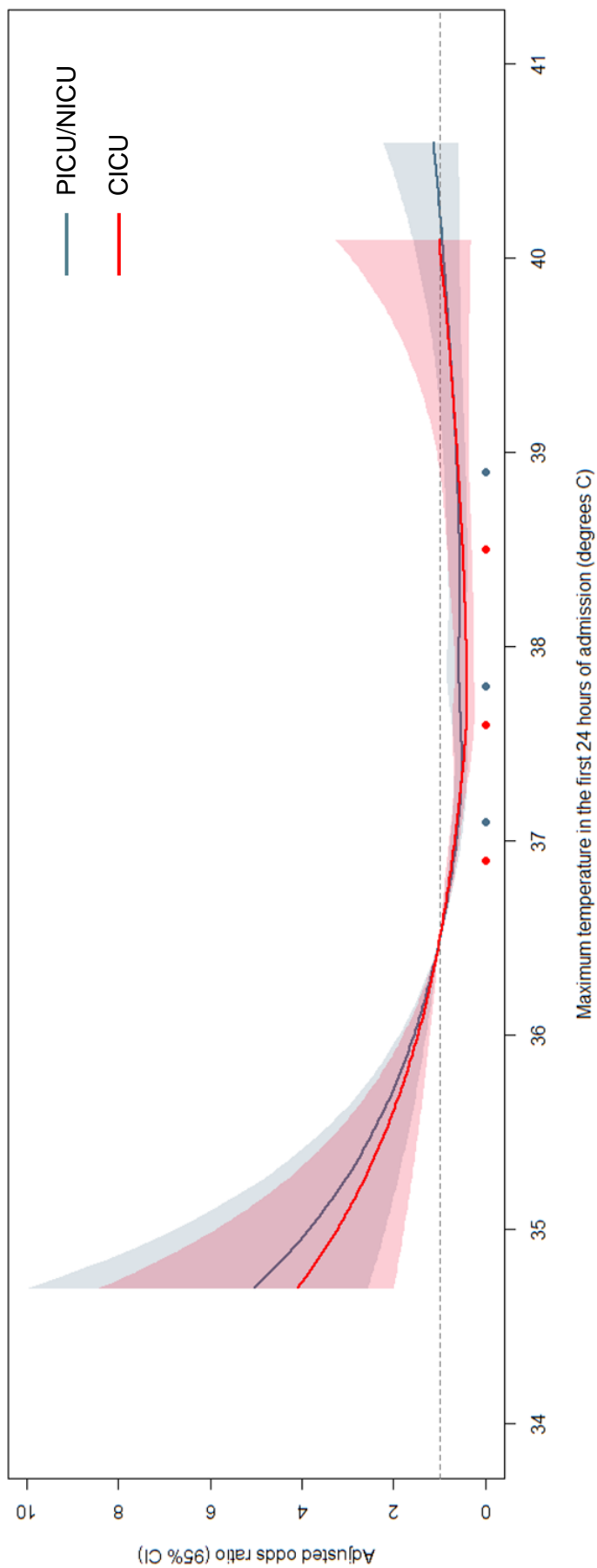


Figure 6.10: Adjusted odds ratio of death according to maximum temperature in the first 24 hours of admission for P/NICU and CICU. The blue line shows the odds ratios for children admitted to P/NICU and the red line those admitted to CICU. All odds ratios were calculated relative to the odds ratio when the maximum temperature is 36.5°C and are adjusted for severity of illness using the PIM score. Odds ratios were calculated using restricted cubic splines (3 knots, 4 degrees of freedom). Knots were a priori assigned to the 10th, 50th and 90th centiles of the maximum temperatures in the cohort – this corresponded to 37.1, 37.8 and 38.9°C in the unplanned admission cohort and 36.9, 37.6 and 38.5 in the planned admission cohort.

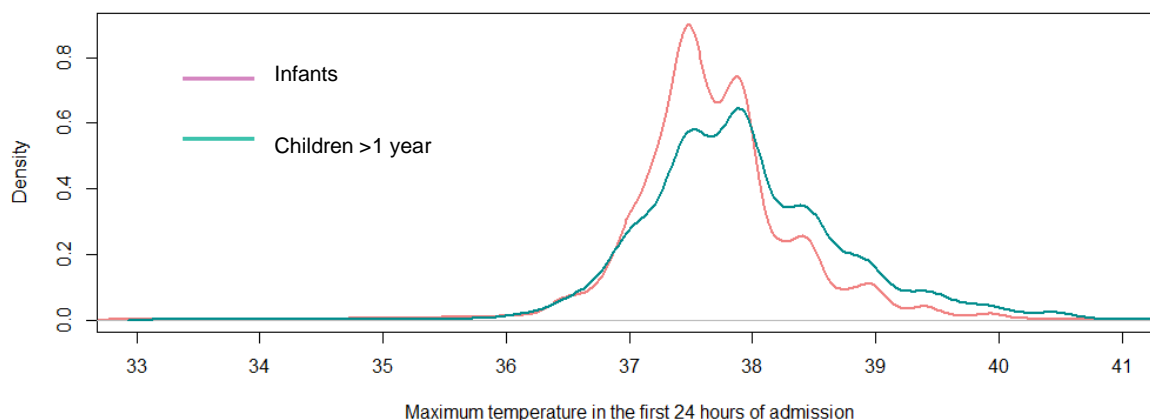


Figure 6.11: Distribution of maximum temperature in the first 24 hours according to age. Data are shown for 5565 children less than 1 year of age (pink) and 4560 children aged 1 year and over (green) admissions. There is a significant difference in the distributions following the Mann-Whitney test ($W=1.04 \times 10^7$, $p\text{-value}<2.2 \times 10^{-16}$).

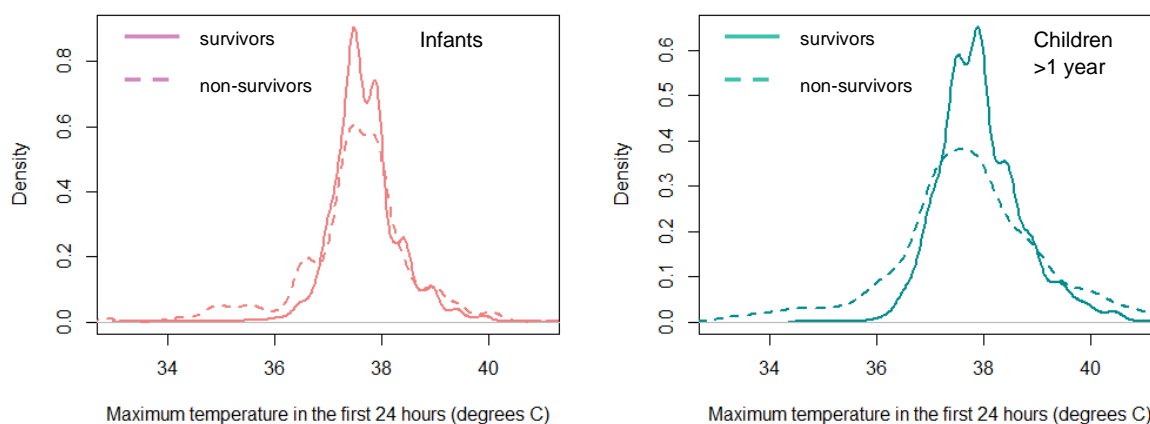


Figure 6.12: Distribution of maximum temperature in the first 24 hours for survival to discharge according to age. Data are shown for survivors (continuous line) and non-survivors (dashed line) in (a) children less than 1 year of age (left, pink) and (b) children 1 year and over (right, green). There were 5399 survivors and 290 non-survivors amongst children <1 year and 4494 survivors and 196 non-survivors amongst children 1 year and over. There is a significant difference between the maximum temperatures of survivors and non-survivors for children <1 year ($p\text{-value}=0.046$) and children 1 year and over ($p\text{-value}=0.003$) following the Mann-Whitney test.

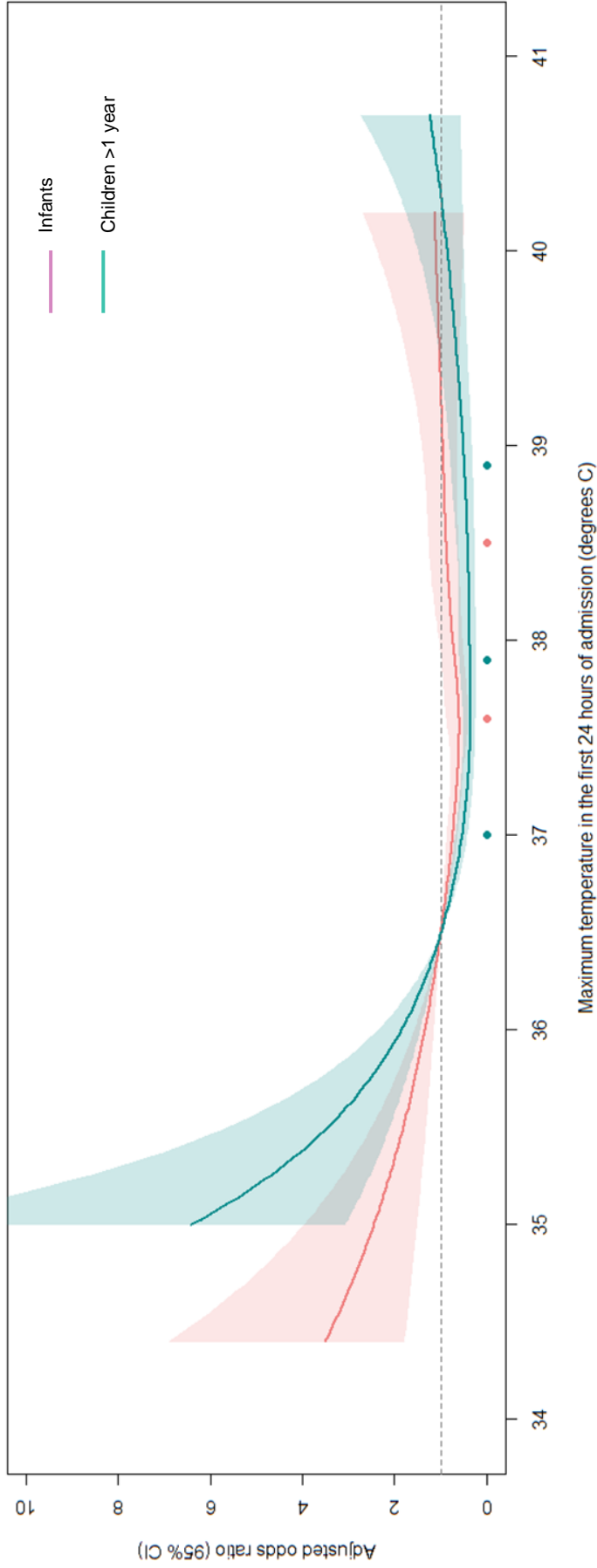


Figure 6.13: Adjusted odds ratio of death according to maximum temperature in the first 24 hours of admission for infants and older children. The pink line shows the odds ratios for children less than 1 year of age and the green line for children 1 year and over. All odds ratios were calculated relative to the odds ratio when the maximum temperature is 36.5°C and are adjusted for severity of illness using the PIM score. Odds ratios were calculated using restricted cubic splines (3 knots, 4 degrees of freedom). Knots were a priori assigned to the 10th, 50th and 90th centiles of the maximum temperatures in the cohort – this corresponded to 37.0, 37.6 and 38.5°C in the unplanned admission cohort and 37.0, 37.9 and 38.9 in the planned admission cohort.

6.4.2 Association between Tmax and death in the FEAST cohort

The FEAST cohort included 3170 children. Temperature data were available for all but 2 children. Temperature measurements were taken at randomisation, and then at 1, 4, 8 and 24-hours post-randomisation. Of the 3170 children, 2855 survived and 315 died (mortality rate 9.9%). The distribution of Tmax was not normally distributed (Kolmogorov-Smirnov D-statistic 0.05, p-value= 8×10^{-4}). The median Tmax was 38.7°C, with an IQR of 38.0-39.4°C. This is significantly different to the Tmax from the GOSH PICU cohort, who have significantly lower temperatures (p-value $<2.2 \times 10^{-16}$) (Figure 6.14).

The distribution of Tmax is shown for survivors and non-survivors is shown in Figure 5.15. The median Tmax for survivors was 38.7°C, IQR 38.0-39.4°C; for non-survivors the median was 38.2°C, IQR 37.1-39.1°C. As with the UK cohort, there was significant difference in the Tmax of survivors and non-survivors (Mann-Whitney $W=5 \times 10^5$, p-value= 2.4×10^{-14}). The ROC curve for Tmax is shown in Figure 5.15: the area under the curve is 0.63 (95% CI 0.59-0.67). As seen with the ICU populations in children, Tmax is a poor predictor of mortality in any single direction.

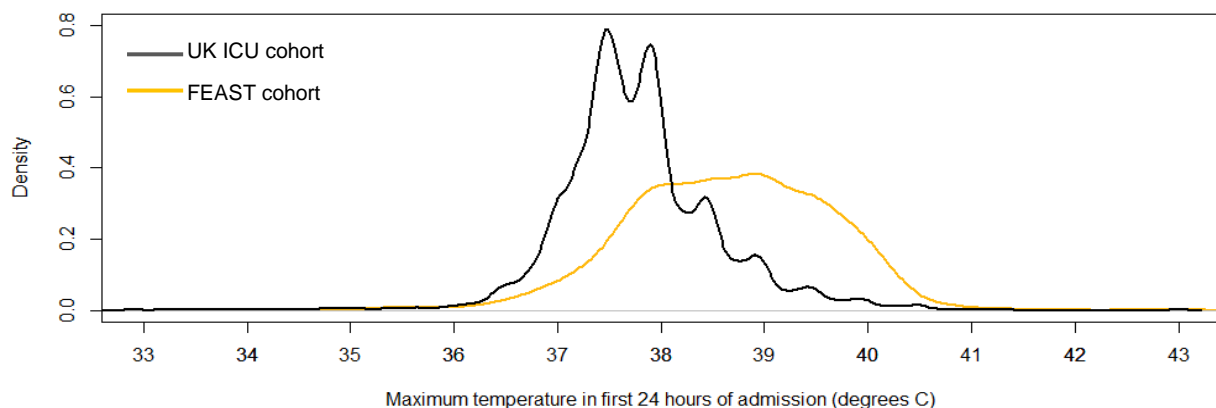


Figure 6.14: Distribution of maximum temperature in the first 24 hours of admission in children recruited to FEAST compared to those admitted to ICU. Data from (a) children recruited to the FEAST study (n=3168, gold), compared to (b) children admitted to ICU in the UK (n=10125, grey). The FEAST cohort has a significantly higher maximum temperature in the first 24 hours. (Mann-Whitney test W-statistic 2.5×10^7 , p-value $<2.2 \times 10^{-16}$)

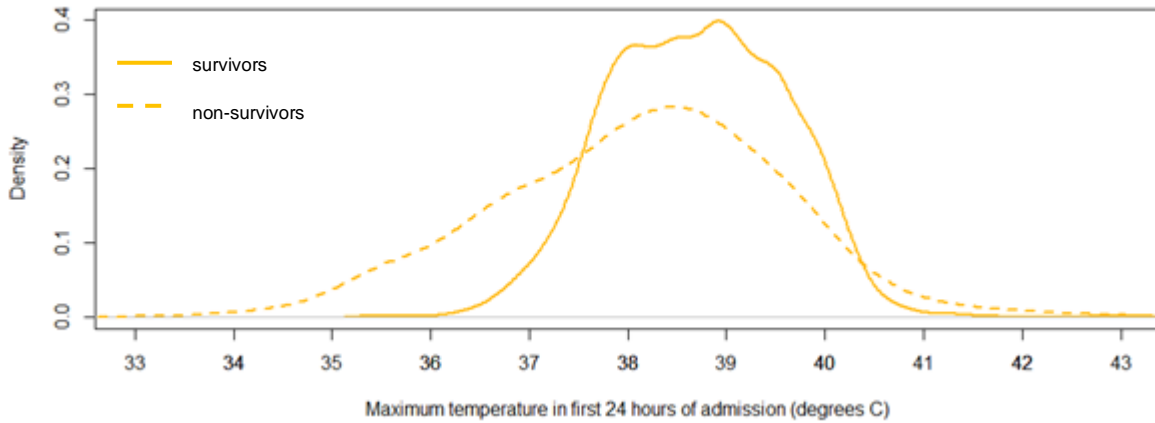


Figure 6.15: Distribution of maximum temperature in the first 24 hours according to survival at 48 hours in FEAST. Tmax is shown for 2855 survivors (continuous line) and 315 non-survivors (dashed line) recruited to the FEAST study. There is a significant difference in the distributions following the Mann-Whitney test (p -value= 2.4×10^{-14}).

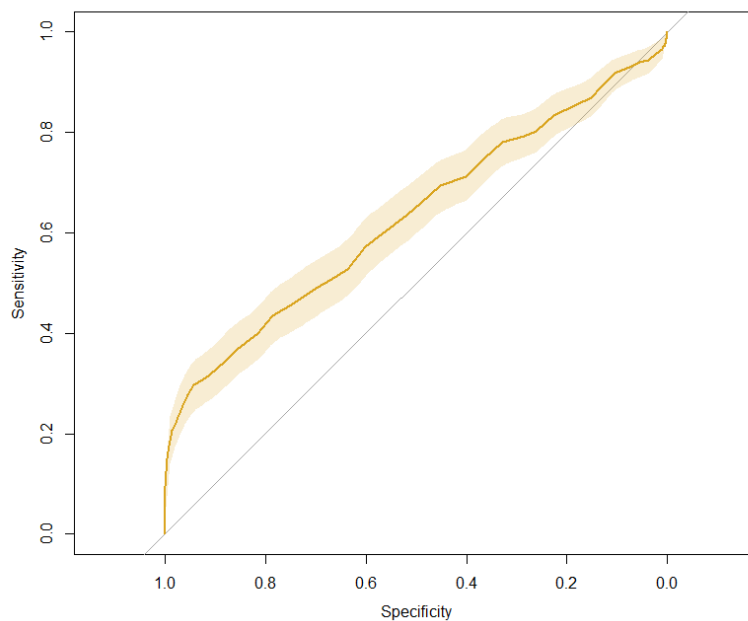


Figure 6.16: Receiver operator characteristic curve for maximum temperature in the first 24 hours for children recruited to the FEAST study (n=3168). The shaded area represents the 95% confidence interval. The area under the curve is 0.63 (95% CI 0.59-0.67).

To determine the better indicator of risk of mortality, the bedside PET score, developed using the FEAST cohort and a calculated PIM derived risk of mortality at recruitment were

compared. The PET score was modified to remove the temperature component (in the PET score a temperature $<37^{\circ}\text{C}$ at recruitment increased the PET score by 1). The ROC curves for the modified PET score and the PIM risk of mortality are shown in Figure 6.17. The modified PET score was the better predictor of the risk of mortality in the FEAST cohort, with an area under the curve of 0.79 (95% CI 0.77-0.82).

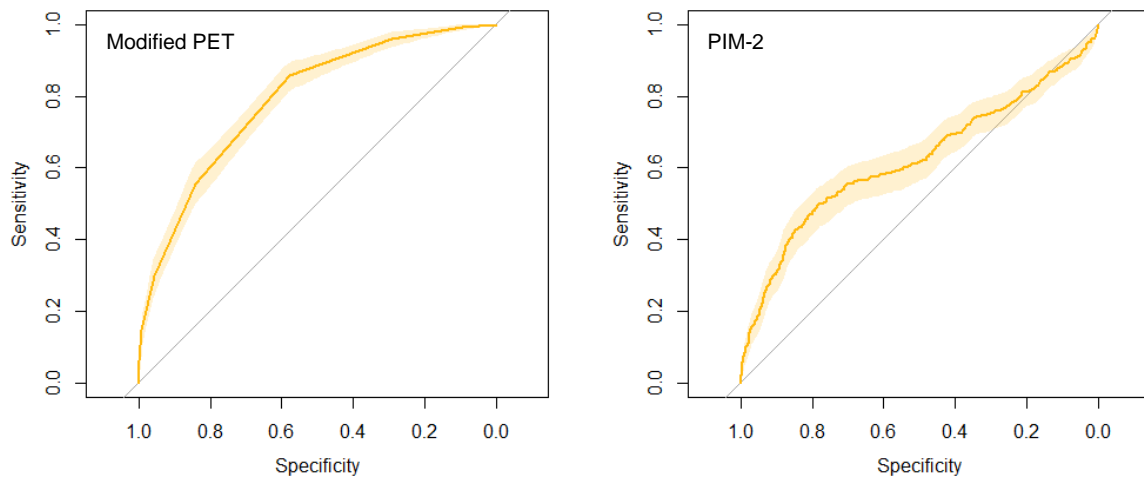


Figure 6.17: Receiver operating characteristic (ROC) curves for (a) the modified PET score, with the temperature component removed, and (b) the calculated PIM risk of mortality for the FEAST cohort. The area under the ROC curve for the modified PET score is 0.79 (95% CI 0.77-0.82) , while that for the PIM risk of mortality is 0.62 (95% CI 0.58-0.66). There is a statistically significant difference between the two curves using DeLong's method for comparison (p-value 1.99×10^{-12}).

The odds ratios of death for the FEAST cohort for Tmax were calculated using logistic regression. Tmax was transformed using a 3-knot restricted cubic spline, with knots at 37.5, 38.7, 39.9 (corresponding to the 10th, 50th and 90th centile for the FEAST cohort). The modified PET score was used in the logistic regression model to adjust for risk of death. The adjusted odds ratios, relative to odds ratios for a tmax of 36.5°C are shown in Figure 5.18. The same curve for the GOSH PICU cohort is overlaid. The adjusted odds ratio of death is lowest at a Tmax of 38°C , although the adjusted odds ratios of death are lower for all values of $\text{Tmax} > 36.5^{\circ}\text{C}$ when compared to a Tmax of 36.5°C (Figure 6.18).

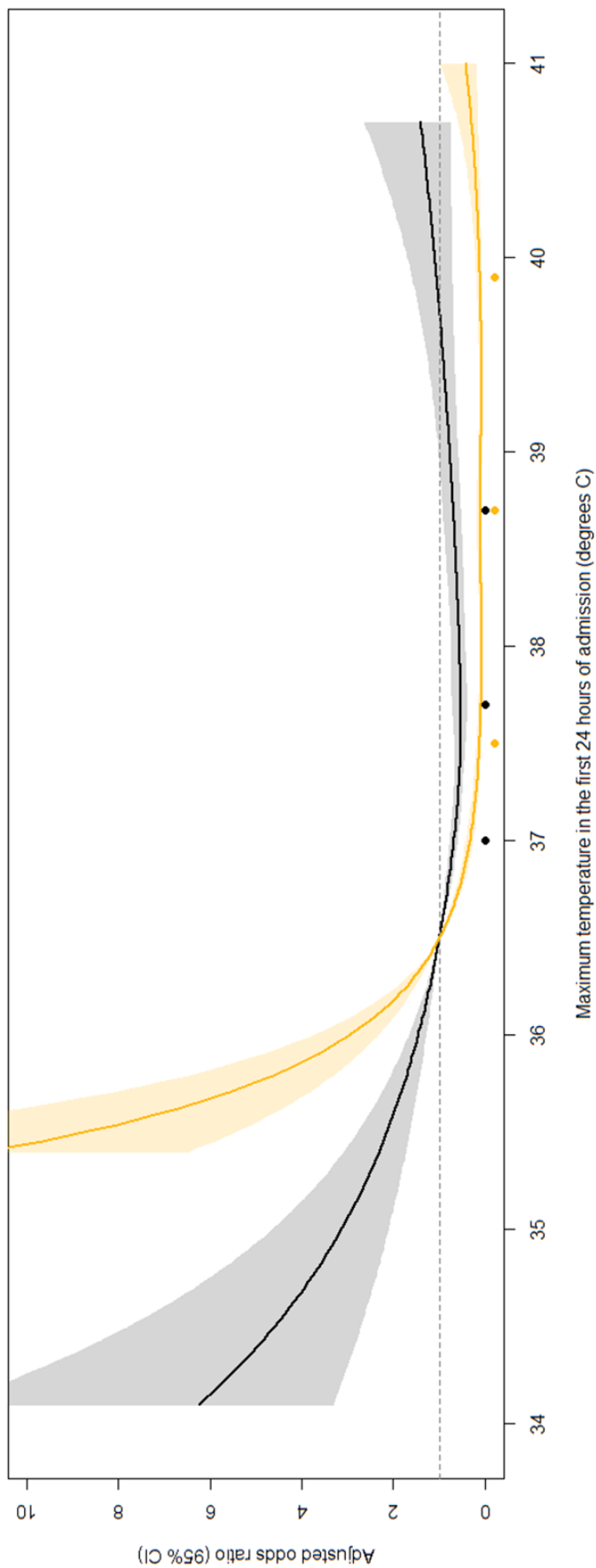


Figure 6.18: Adjusted odds ratio of death according to maximum temperature in the first 24 hours of admission for children recruited to the FEAST trial and those admitted to ICU in the UK. The gold line shows the odds ratios for children enrolled to the Fluid as Expansive Supportive Therapy (FEAST). The grey line shows the odds ratios for children admitted to ICU at Great Ormond Street from 2012-17. All odds ratios were calculated relative to the odds ratio when the maximum temperature is 36.5°C. The odds ratios for the FEAST cohort are adjusted for using the Paediatric Emergency Triage (PET) score, modified by removal of the temperature component (therefore scored out of 9). The odds ratios for the ICU cohort are adjusted for using the PIM score. Odds ratios were calculated using restricted cubic splines (3 knots, 4 degrees of freedom). Knots were a priori assigned to the 10th, 50th and 90th centiles of the maximum temperatures in the cohort – this corresponded to 37.5, 38.7 and 39.9 in the FEAST cohort and 37.0, 37.7 and 38.7°C in the ICU cohort (dots above the y-axis).

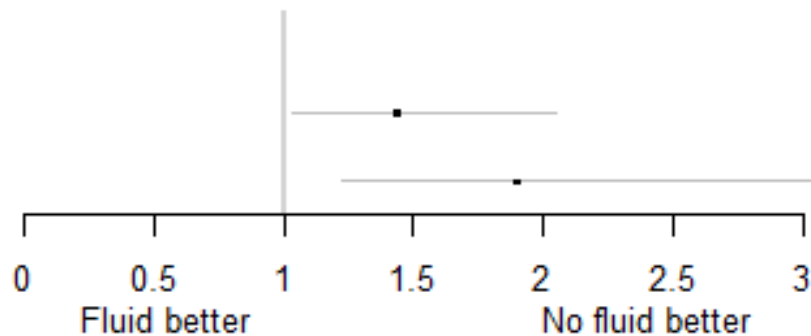
6.4.3 Analysis of the effect of fever on the FEAST trial results

Children randomised to receive either 0.9% sodium chloride or 4.5% human albumin solution were combined for this analysis – 2126 children had been randomised to receive fluid boluses. In contrast 1044 children were randomised to receive no fluid bolus. At randomisation, 1371 children did not have a fever, compared to 1791 who did have fever; 8 children did not have temperature recorded at baseline (3 children were randomised to receive no fluid bolus and 5 children to receive a fluid bolus).

The mortality rate for children with no fever was 194/1371 (14.2%); for those with fever was 118/1791 (6.7%). The odds ratio for receiving a fluid bolus for children with no fever at randomisation was 1.44 (95% CI 1.03-2.05); for children with fever it was 1.90 (95% CI 1.23-3.04). This suggests that fluid was significantly associated with harm in both those with and without fever at randomisation. When the modified PET score was included in the model, the odds ratios for receiving a fluid bolus was 1.22 (95% CI 0.85-1.77) for those with no fever at randomisation, and 1.75 (95% CI 1.09-2.88) for those with fever. This would suggest that fluid was significantly associated with harm in those with fever but not so in those without a fever. These results are summarised in figure 5.19 and table 6.1. The I^2 statistic was 0% using a random effects model, suggesting a low level of inconsistency between the arms.

Given that the confidence intervals around the odds ratio estimates overlap between those with and without fever at randomisation, it is unlikely that the difference between the two models are statistically significant. The logistic regression model was repeated with fever as an interaction term for fluids on survival – the interaction term was not significant, supporting the above result.

A	No fluid	Fluid	OR (95% CI)
	no. of deaths/no. of children (%)	no. of deaths/no. of children (%)	
No fever	51/451 (11.3)	143/920 (15.5)	1.44 (1.03-2.05)
Fever	25/590 (4.2)	93/1201 (7.7)	1.90 (1.23-3.04)



B	No fluid	Fluid	OR (95% CI)
	no. of deaths/no. of children (%)	no. of deaths/no. of children (%)	
No fever	51/451 (11.3)	143/920 (15.5)	1.22 (0.85-1.77)
Fever	25/590 (4.2)	93/1201 (7.7)	1.75 (1.09-2.88)

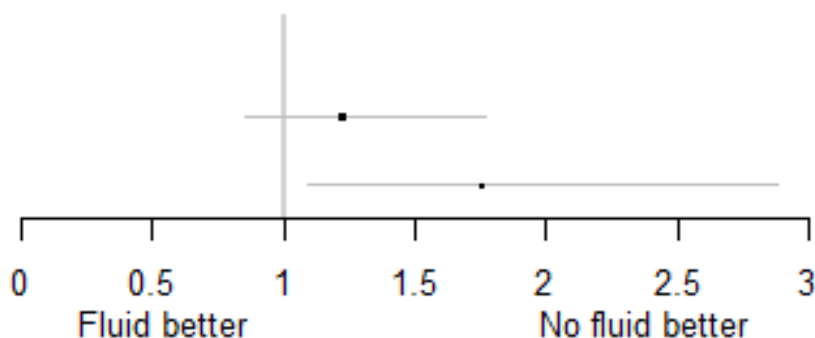


Figure 6.19: Forest plot summarising odds ratios for children with no fever and fever at randomisation in the FEAST trial. (A) The top figure shows the odds ratios without adjustment: the odds ratio was 1.44 (95% CI 1.03-2.05) in favour of the no fluid bolus arm in the no fever group. In the fever group the odds ratio was 1.90 (95% CI 1.23-3.04) also in favour of the no fluid arm. (B) The bottom figure shows the corresponding odds ratios following adjustment for the bedside PET, excluding the temperature variable. In the no fever group, the odds ratio was 1.22 (95% CI 0.85-1.77) suggesting fluid was not associated with mortality. In the fever group the odds ratio was 1.75 (95% CI 1.09-2.88) in favour of the no fluid arm. Given the overlapping confidence intervals however, this effect is unlikely to be statistically significant. The I² statistic was 0%.

Models	Odds Ratios (95% CI)	p-value
A		
<i>No fever</i>		
Fluid	1.44 (1.03-2.04)	0.04
<i>Fever</i>		
Fluid	1.90 (1.23-3.04)	0.01
B		
<i>No fever</i>		
Fluid	1.22 (0.85-1.77)	0.30
Modified PET score	2.20 (1.93-2.52)	<2 x 10 ⁻¹⁶
<i>Fever</i>		
Fluid	1.75 (1.09-2.88)	0.02
Modified PET score	2.31 (2.00-2.69)	<2 x 10 ⁻¹⁶
C		
Fluid	1.21 (0.84-1.76)	0.30
Fever	0.50 (0.29-0.84)	0.01
Modified PET score	2.25 (2.04-2.49)	<2 x 10 ⁻¹⁶
Fluid*Fever	1.44 (0.79-2.66)	0.24

Table 6.1: Table showing the odds ratios for 48-mortality with and without fluid resuscitation according to fever at randomisation in the FEAST study. (A) Uni-variable model with odds ratios for those with and without fever – fluid associated with increased 48-hour mortality in both groups. (B) Odds ratios from logistic regression models with the modified PET score (excluding the temperature variable) and whether randomised to receive fluid, for children with or without fever. Fluid associated with increased mortality in those with fever but not those without fever at randomisation. (C) Odds ratios from a logistic regression model with fever and fluid resuscitation as an interaction term, to explore the effect of fluid resuscitation in fever. The odds ratio for the interaction term although >1 has a wide 95% confidence interval including 1 i.e. the interaction is not statistically significant.

6.5 Discussion

6.5.1 Summary of results

Data from 10125 admissions to ICU at Great Ormond Street Hospital were analysed to understand the association between temperature in the first 24 hours of admission and mortality. The analyses of these data suggest:

- i. There is a significant difference between the maximum temperature in the first 24 hours of admission between survivors and non-survivors. This is seen in children admitted to general PICU/NICU and CICU, and children less than 1 year of age and those 1 year and over. There was no difference between Tmax for survivors and non-survivors following planned admissions. In all cases, non-survivors tended to have lower temperatures in the first 24 hours.
- ii. The ROC curves show that the maximum temperature in the first 24 hours of admission alone was a poor predictor of mortality. This suggested there was no proportional relationship between Tmax and mortality in any direction.
- iii. The multivariable analysis identified a U-shaped association between the maximum temperature in the first 24 hours of admission and mortality i.e. the risk of mortality increased with both low and high values of Tmax. The risk of mortality was greatest for those who had Tmax <36.5°C.
- iv. The multivariable analyses identified the Tmax values associated with the lowest risk of death. In the whole GOSH cohort this was 37.6°C, and 38°C for children following unplanned admissions.

Temperature data from 3162 children recruited to the FEAST trial were also analysed for comparison. These data suggest:

- (i) Children in the FEAST cohort had higher maximum temperatures in the first 24 hours post-randomisation compared to the GOSH ICU cohort, with a median temperature of 38.7°C (cf 37.7°C in the GOSH cohort).
- (ii) As with the GOSH ICU cohort, non-survivors in the FEAST cohort had a significantly lower Tmax compared to survivors. Temperature was still a poor predictor of mortality based on the ROC curve.
- (iii) Following multivariable analysis, the risk of mortality rises steeply for Tmax values less than 36.5°C, more so than in children in the GOSH ICU cohort. The lowest risk of death was associated with a Tmax of 38.0°C, but the risk of death was not significantly different for most Tmax values between 36.5°C and 40.0°C.
- (iv) Regardless of presence or absence of fever (temperature $\geq 38^{\circ}\text{C}$) at randomisation, mortality was lower in those randomised to receive no fluid compared to those who received 0.9% sodium chloride or 4.5% human albumin boluses. The odds ratios were not significantly different for those with or without fever. When baseline severity of illness was accounted for using the modified bedside PET score, randomisation to receive fluid was not associated with 48-hour mortality in those without fever, while it was in those with fever. However, the difference in odds ratios were not statistically significant.

6.5.2 Hypothesis testing and Implications of the findings

The UK PICU cohort demonstrates a U-shaped association between maximum temperature in the first 24 hours of admission and PICU mortality. Maximum temperature in the first 24 hours was used to examine the association between temperature and mortality. The shape of the association between Tmax and mortality in the GOSH ICU cohort resembles that of the adult data. Young et al used Tmax divided into 0.5°C categories in a logistic regression analysis. The use of restricted cubic splines allows the use of a continuous variable not expected to have a linear relationship with the risk of mortality. The

risk of this may be in overfitting data, especially for small sized cohorts. Although the UK cohort was large with over 10000 admissions, this was still small compared to Young's adult population (more than 600000). Nevertheless, the shape of the association between Tmax and risk of mortality was the same following both sets of analyses.

The use of adjusted odds ratios relative to a reference value (in this case a Tmax of 36.5°C) informs us of the temperature associated with the lowest risk of death, adjusted for the overall risk of death. This is the nadir of the curve. A Tmax of 36.5°C was chosen as Young et al used the category of 36.5-36.9°C as their reference category. For the overall GOSH PICU cohort the lowest adjusted odds ratio of death is associated with a Tmax of 37.6°C. This is not in the febrile range: fever may not be beneficial for all children. Data on infection status was not available. However, to try and dissociate children the effect of fever on those with infections and non-infective illnesses, I analysed the sub-groups who had planned and unplanned admissions. The assumption is that children with unplanned admissions are more likely to have infections. In this cohort the Tmax associated with the lowest risk of death was 38°C, compared to 37.3°C in the planned admission category. Most of the children with planned admissions will have been admitted post-surgery, primarily cardiac surgery (74% of children admitted the cardiac ICU were following planned surgery compared to 36% on PICU/NICU), and therefore are likely to have sterile inflammation. This difference supports the hypothesis that a fever grade temperature is beneficial in children with infections.

The lowest risk of death is associated with a temperature of 37.8°C in the cardiac population compared to 37.4°C in general PICU/NICU. Temperature may be a surrogate of cardiac output and function in children on the cardiac ICU, and it may be this association that is being measured. Alternatively, this may be due to the inclusion of the premature neonatal population in the general PICU/NICU population, in whom temperature control is immature and carefully regulated through environmental control in incubators. Prematurity or weight was not accounted for in the analysis – although just over 12% of the population had a corrected gestational age <37 weeks at admission and <1% had a corrected gestational age

<27 weeks at admission (those with the most immature thermoregulation) (Table 2.1). However, caution must be exercised in interpreting a difference between these two sub-groups as no significance testing was undertaken. There is little difference in the optimal T_{max} for children less than 1 year of age and 1 year and over. Despite this, the shapes of the curves differ, with a much steeper increase in risk of death in children 1 year or over when the T_{max} is <36.5°C. In children less than 1 year of age, which includes premature neonates, the curve was shallower, suggesting a lower relative risk of death when cold. This is a complex relationship to interpret: children less than 1 year may require more energy to generate a fever given the higher surface area to weight ratio, but a large proportion of these children would have formed the CICU population. Conversely, many of these children are also nursed in incubators or under radiant heaters – therefore, some of the T_{max} values may be a result external control rather than a reflection of physiological processes.

The distribution of T_{max} in the UK ICU cohort consistently shows a bimodal density distribution, including in all the sub-groups, although only in survivors and not non-survivors. This may reflect yet to be defined inflammatory phenotypes in critically ill children, although source of measurement may explain the distribution – for example, those who had continuous measurements had a greater likelihood of capturing a higher temperature (due to sampling frequency) or due to a bias in the differences in measurements between devices (oesophageal versus axillary as predominant modes of thermometry).

The sub-Saharan African children show a different optimal temperature for survival to the UK PICU cohort. In the FEAST cohort T_{max} had a greater relative effect on mortality than in ICU children. This is implied by the presence of a temperature variable in the PET score but not the PIM score. The FEAST cohort only included children with infection. Many of these infections would be different to those seen in UK PICUs – for example, malaria, tuberculosis, and other tropical diseases, where disease specific treatment may be available, but mortality is high. As described in Chapter 1, the main beneficial effect of fever has been

shown to be immunological. Therefore, the greatest effect on mortality may be in children with infection rather than sterile inflammation.

The effect of the environment may explain the different risk of death associated with maximum temperature between the GOSH PICU and the FEAST cohorts. In ICU the environmental temperature is closely regulated to 18-20°C. Ventilator air is heated to a certain temperature and intravenous fluids are at usually at room temperature. Children on extracorporeal circuits such as for renal replacement therapy or extra-corporeal life support have their blood warmed. Therefore, to generate a fever above this temperature regulation is likely to require greater energy consumption: heat production is required to overcome the limitation of external control. In the FEAST cohort, where no ICU provision was available and the environmental temperature was not regulated and high, it is possible that fever could be generated with relatively less heat production. In this case the benefit of generating fever grade temperature may have outweighed the energy cost.

There is an argument against this inference: children in the UK ICU cohort would have conserved energy through ICU interventions – mechanical ventilation, sedation, renal support. This may have made energy available for heat production to generate a fever *if* fever was beneficial. In the FEAST cohort, given that energy would have been scarce (relatively poor nutritional status, plus the lack of organ support), any energy conservation may be of benefit. This is part of the Central Governor Hypothesis [Humphrey and Skoyles, 2012]. The hypothesis proposes that as an organism the human being can adapt to use available resources to maximise the chance of survival. Therefore, if energy is scarce, the use of energy in heat production for a fever may compromise basic functions such as breathing and digestion. In such a case it may prove more beneficial to not mount a fever. When the energy becomes available, then the fever can be generated for the added immune benefits. Following this hypothesis, the GOSH PICU would be better placed to generate a fever for a survival benefit than the FEAST cohort. Instead, the GOSH PICU cohort had a lower T_{max} associated with survival compared to the FEAST cohort.

The results above do not wholly contradict the Central Governor Hypothesis for several reasons: (i) The GOSH PICU cohort did not all have infections, whereas those in the FEAST cohort did. Therefore, the relative benefit of a fever may have been greater in the FEAST cohort. The types of infections (bacterial versus viral) and immune status may also determine the relative benefit of fever in each cohort; (ii) as stated, the relative amount of energy needed to generate a fever in the GOSH PICU cohort may have been greater against the multiple environmental temperature regulations in an ICU. This could tip the balance against generating a fever despite the energy conserved through ICU interventions. In the FEAST cohort, heat conservation in a warmer environment may not require high levels of heat production to generate a fever; (iii) The ICU interventions may have had a therapeutic effect, for example, in reduction of tissue hypoxia and shock that the infection may have generated. This may diminish the relative importance of fever in providing a survival benefit when fighting infection. (iv) There may also be an effect of time of presentation to hospital: in PICU cohort fever occurred early but largely disappeared after the first 48 hours. This may mark recovery from infection. In the FEAST cohort presentation to hospital was likely to be later due to resource availability. The higher temperatures may represent an ongoing immune response with higher temperatures to provide an advantage against infection.

What is very clear from both cohorts and all the subgroups is that a T_{max} below 36.5°C is associated with an increased risk of death. This rises almost exponentially for temperatures below 36.5°C . Moderate hypothermia as a therapeutic intervention (targeted temperature $33\text{-}34^{\circ}\text{C}$) was rarely used in the GOSH ICU cohort because of the evolving literature against the previously touted benefits of this strategy in the context of brain hypoxia. Low temperatures were more likely a marker of the inability to appropriately thermoregulate. The effect was seen despite adjusting for the severity of illness using PIM or PET. It is difficult to know if this is a marker of the energy state i.e. inability to generate temperatures in the normal range, or more so, mount a fever. Neither PIM nor PET may be able to adequately reflect the energy

state, although the correlation with severity of illness should be expected. It is still possible that temperature has an intrinsic benefit to the immune response (or other physiological mechanisms such as haemodynamics) in all critical illness. The use of cooling below 36.5°C, even though it may reduce vasopressor need for example, cannot be supported by these results to provide a mortality benefit. Long term outcomes in survivors, such as neurodevelopmental benefits of hypothermia cannot be discounted.

Fever at randomisation had no effect on the outcome according to interventions in the FEAST trial. Were fever to increase the oxygen debt in critically ill children, leading to mortality, then increasing oxygen delivery may ameliorate this debt and improve the risk of survival. Fluid is given to increase tissue oxygen delivery, by improving pre-load and therefore cardiac output. In the FEAST trial, fluid bolus therapy with 0.9% sodium chloride or 4.5% human albumin solution was shown to increase mortality at 48 hours when compared to no fluid. This relationship was preserved when children with and without fever at randomisation was analysed separately. However, when PET scores, as a marker of severity of illness were accounted for in a multi-variable model, the mortality effect of fluid in those with no fever was not seen; in those with fever, fluid was still associated with harm. The difference between the odds ratios was not be statistically significant: this may be due to the lower proportion of children without fever, but a higher mortality rate within this group, regardless of whether they received fluid or not. Using temperature as a continuous variable, rather than dichotomised into fever and no fever, may help with this analysis. Post-hoc logistic regression analysis using 48-hour mortality as the outcome measure, temperature as a continuous independent variable following restricted cubic spline transformation (using knots at 10th, 50th and 90th centiles as previously described) and the modified PET score as a confounder, was carried out for the arms randomised to receiving fluid or no fluid. The results are shown in figure 6.20, The greatest harm associated with fluids seems to be

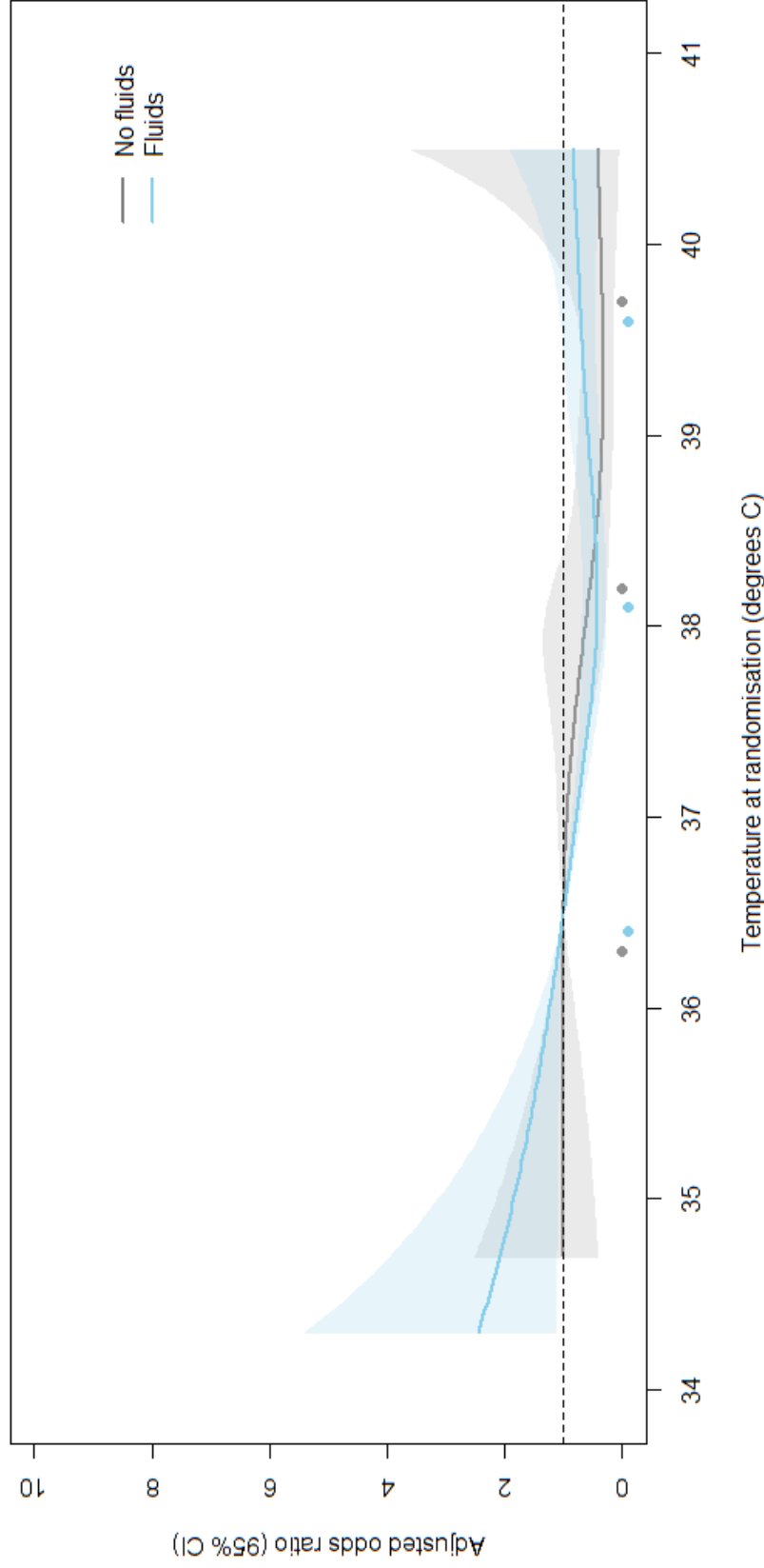


Figure 6.20: Adjusted odds ratio of death according to temperature at randomisation for children enrolled to the Fluid as Expansive Supportive Therapy (FEAST). The adjusted odds ratios were calculated using separate logistic regression models in children who were (a) randomised to receive no fluids (grey line) and (b) children randomised to receive fluids (blue line), relative to the odds ratio when the maximum temperature is 36.5°C. The odds ratios are adjusted for using the Paediatric Emergency Triage (PET) score, modified by removal of the temperature component (therefore scored out of 9). Odds ratios were calculated using restricted cubic splines (3 knots, 4 degrees of freedom). Knots were a priori assigned to the 10th, 50th and 90th centiles of the maximum temperatures in the cohort – this corresponded to 36.3, 38.2 and 39.7 in the no fluid arm and 36.4, 38.1 and 39.6°C in fluid arm (dots above the y-axis).

associated in those with temperatures $<36.5^{\circ}\text{C}$ i.e. those with no fever. In the remaining children there was little difference between the adjusted odds ratios, although at higher temperatures, the adjusted odds ratios started to increase in those who were randomised to fluids compared to those who were not.

The recent TRACT trial hinted at a similar result: in severely anaemic children in Sub-Saharan Africa, children with fever had better outcomes when transfused with lower volume of blood compared to those transfused with a higher volume of blood. Those without fever showed the reverse relationship. Thus, trying to increase oxygen delivery during fever with fluid or blood may not improve outcome. This is counter to what would be expected if fever created an imbalance in oxygen consumption and delivery: fluid would augment oxygen delivery reducing the imbalance. One problem not accounted for is the assumption that fluid bolus therapy increases oxygen delivery. This may not be the case for two reasons (1) the FEAST cohort had high levels of chronic anaemia. Fluid bolus therapy may serve to dilute haemoglobin and not increase oxygen delivery to tissues. However, in secondary analysis of the FEAST data, no difference in the effect was seen across a range of threshold haemoglobin levels at randomisation: those with severe anaemia showed equal harm from fluid as those with mild or no anaemia [Kiguli 2015]. (2) A fluid bolus may only increase stroke volume if the myocardium is able to respond (i.e. on the up-slope of the Starling curve). If the heart is failing in these children, then further fluid may not increase oxygen delivery but instead precipitate myocardial failure. This may be more likely in children with fever given the increased heart rate (leading to reduced coronary perfusion time) and without the supportive intensive care therapies (ventilation, inotropy) to augment myocardial work. The lack of a fever may indicate decompensation of myocardial function beyond recovery – with an inability to generate a fever or to respond to fluids. The death rate in the non-febrile cohort for those who were and were not randomised to receive fluids was higher than those who received fluids and had fever. Both Maitland et al in their planned analysis of mechanisms of death, and Levin et al in their more controversial post-hoc re-analysis of the

trial results described a short-term favourable response to fluid in the fluid arms [Maitland 2013; Levin 2019]. Maitland described a higher percentage of deaths with cardiovascular shock as the terminal event compared to respiratory or neurological failure. Levin et al used cluster analysis to identify a high-risk cluster with initial poor cardiovascular status, low haemoglobin and high lactate (i.e. a cluster with the greatest evidence of an oxygen debt through an oxygen delivery and consumption imbalance): in these children fluid was associated with harm, although given the smaller numbers, there was overlap of the confidence intervals in the hazard ratios. This supports the hypothesis of fluid causing cardiovascular failure in those with worse cardiovascular function or increased cardiovascular compensation. Neither author however considered the effect of temperature.

6.5.3 Limitations

The use of retrospective analysis of data from both the GOSH PICU cohort and the FEAST trial have certain limitations:

- (1) The main limitation with such a retrospective analysis is that it detects association but not causation. Therefore, it is impossible to say that temperature has a direct effect on mortality in acute illness, even in infection. There are no data regarding interventions undertaken in ICU. The maximum temperature may be an indicator for an intervention: for example, in a propensity score matched retrospective analysis, Suzuki et al found that use of paracetamol in ICU was associated with reduced in-hospital mortality [Suzuki 2015]. It is possible that higher temperatures were associated with paracetamol use and it was this that has the effect on mortality seen in children with fever. It would be possible to test the hypothesis that paracetamol use in the first 24 hours is associated with decreased mortality. This was not undertaken for the following reasons: (a) maximum temperature in the first 24-hours has a very weak absolute association with mortality – the aim was to identify the

maximum temperature which was associated with the lowest risk of mortality; (b) as paracetamol is used widely, often as analgesic, detecting an association between paracetamol use and absolute mortality is unlikely. There is a bias in the indication to use paracetamol as demonstrated in Chapter 2 – not all children with fever were treated. Therefore any association between paracetamol and mortality would require further analysis of why they received paracetamol; (c) children may have been given paracetamol just prior to or In the days before admission to PICU – biologically this would also have an effect on outcomes (although the same could also be argued about fever prior to PICU admission).

- (2) While I compared the optimum temperatures for the GOSH PICU cohort and the FEAST cohort, the comparison is of the risk of death relative to a Tmax of 36.5°C in the first 24 hours. It was not possible to compare the absolute risk of death associated with temperatures. The cohorts are not comparable for several reasons: (i) the FEAST cohort only included children with confirmed or suspected infections; (ii) they did not have any intensive care provision. Their crude risk of death was more than twice that of the GOSH PICU cohort. (iii) the adjustment for the risk of death was provided by the PIM score in the GOSH PICU cohort and the PET score for the FEAST cohort; (iv) The PET score was developed in the FEAST cohort and therefore is specific to it (although it has been validated in a different cohort in Sub-Saharan Africa [George 2015]). The reason for comparing the UK population with the FEAST cohort was to compare two cohorts with critical illness, one of who was subjected to ICU interventions. However, there are two major potential confounders: the differences in environmental temperature (to consider the energy required to generate a fever) and differences in the availability of ICU interventions, many of which affect body temperature and energy balance. Ideally a comparison would be made between a cohort of children in the UK with and without ICU provision, but with the same level of critical illness, and two cohorts in a warmer environment, with and without ICU provision (those with ICU provision must not have their or the

environmental temperature regulated). However, these directly comparable populations do not exist and randomisation to a trial to study them may not be ethical given the accepted benefits of ICU interventions.

- (3) Only the maximum temperature in the first 24 hours of admission was used to explore the association between temperature and death. This was to reflect the analysis carried out by Young et al. The relationship between temperature and ICU outcome potentially continuous throughout the ICU stay. The use of maximum temperature reflects a bias towards the hypothesis that fever may be important in the ICU outcome. All the results point to the association between low temperature and mortality. The minimum temperature may be equally, if not more, informative.
- (4) Also, the variation in temperature may be important: the time spent at different temperature may be associated with different levels of energy consumption and/or the immune effects. A brief spike of temperature above 38°C followed by a long period of temperature <36°C may have a different effect compared to having a persistent temperature above 38°C. This sort of analysis of temperature variation is used in comparative biology between species, using something called the heterothermy index [Boyles 2011]. Variation is difficult to judge as the decision to measure a temperature depends on the bedside nurse – for example, temperature may be taken if the patient is felt to be hot. Variation in temperature is also affected by ICU interventions as explained.
- (5) The multivariable models all used restricted cubic spline transformations for temperature as the continuous variable. This assumed that the relationship between Tmax and mortality was non-linear. The knots were chosen a priori at the 10th, 50th and 90th centiles. This assumed that the relationship between Tmax and mortality would vary. This is not an unreasonable assumption, as outcomes are likelier to vary at extremes of physiology, and a method that has been used elsewhere for similar analyses [Mattetore 2019]. The risk of using spline transformations is that the data can be over-fitted. This depends on the number of knots used. In this case, 3-knots

were used to try and minimise over-fitting the model to the data. Other non-linear functions could have been used for regression modelling – the use of cubic splines however is relatively simple, and with 3-knots possibly reduces the risk of overfitting compared to more complex models.

- (6) Only Tmax and PIM (or PET) scores were used in the multi-variable modelling. The sub-group analyses had demonstrated differences in the Tmax between the units, according to age and between planned and unplanned admissions. These could have been considered as confounders in the multivariable model. However, they were not as all the variables either directly or indirectly contribute to the PIM score and therefore problems with collinearity would have become apparent. The PIM score accounts for admissions post-cardiac bypass: most CICU admissions would occur post-bypass, whereas none would have in the P/NICU group. Although age is not directly included in PIM, this would have been reflected in the blood pressure variable [Mattetore 2019]. Whether an admission is planned or unplanned is a variable within the PIM score. Therefore, rather than use these variables in a single multi-variable model, they were analysed as sub-groups.

Regardless, the overall size of the effect of temperature on mortality may be small – certainly in the GOSH PICU cohort. In the development of the PET score in the FEAST cohort, temperature was found to be significant variable in predicting mortality. The optimal temperature may vary between other cohorts, even within the GOSH ICU population. Given the low mortality seen in children admitted to UK PICUs, mortality may not be the ideal outcome measure – instead, time to resolution of infection, or a surrogate such as time to liberation from organ support may be more appropriate. These data were not available retrospectively. Length of stay could be used as a surrogate, but this is often a poor surrogate – there are various reasons that may delay discharge from PICU which may not relate to their initial severity of illness. Post-hoc analysis shows

poor correlation between length of stay amongst PICU survivors (n=9893, although temperature data were available for n=9663) and maximum temperature in the first 24 hours of admission (Figure 6.21). There may be a more complex pattern between length of stay and temperature beyond a simple linear correlation – as seen in Figure 6.22, when children with length of stay ≤ 28 days only are considered. Children with very low temperatures have lower lengths of stay compared to those with very high temperatures. In children with short stays (≤ 4 days), higher temperatures are associated with longer admissions in ICU.

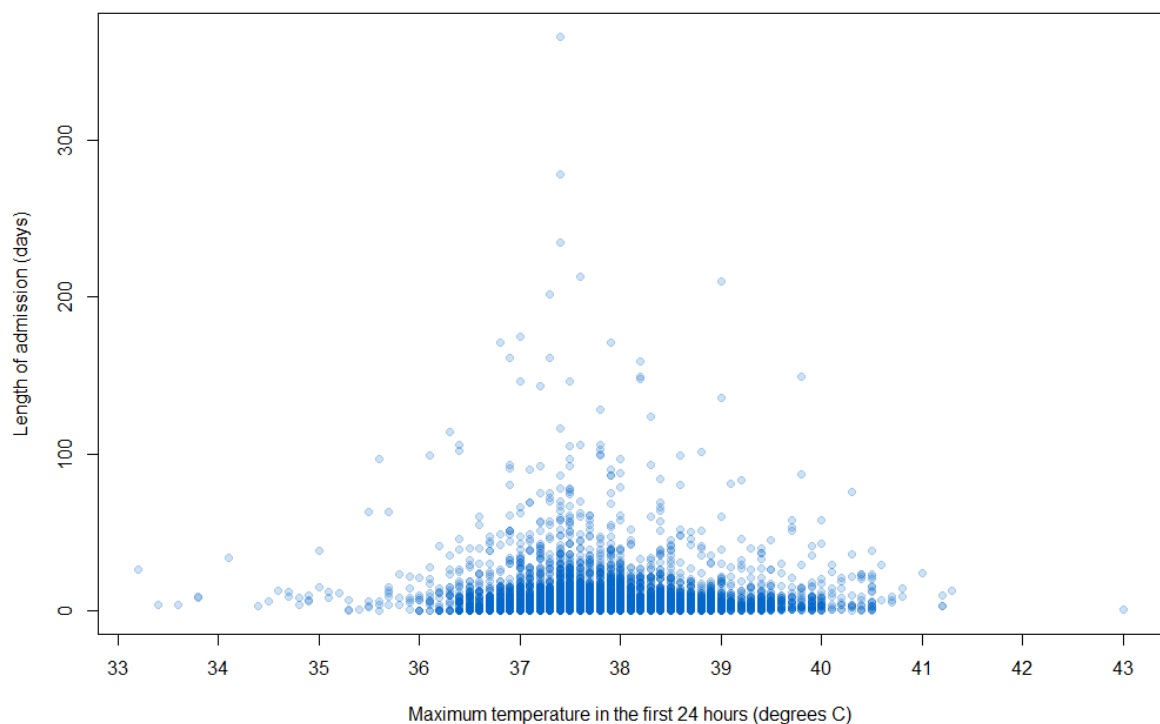


Figure 6.21: Distribution of length of ICU stay for children who survive to ICU discharge, according to the maximum temperature in the first 24 hours of admission. Each dot represents a single admission, the colour intensity represents the number of cases with the same maximum temperature and length of stay (intensity increases with frequency). The distribution does not suggest a strong linear relationship between maximum temperature and length of stay in any direction.

Both these observations may point to competing benefits and costs (risks) of fever: in less serious, self-limiting illnesses, where the child survives and has a short ICU admission, the cost of generating fever may exceed the benefit, and fever is not generated. For more serious illnesses, the mortality benefit of fever exceeds the cost and therefore fever is afforded. However, these are merely hypotheses and are best tested prospectively, using length of intensive care support rather than length of stay as the outcome variable.

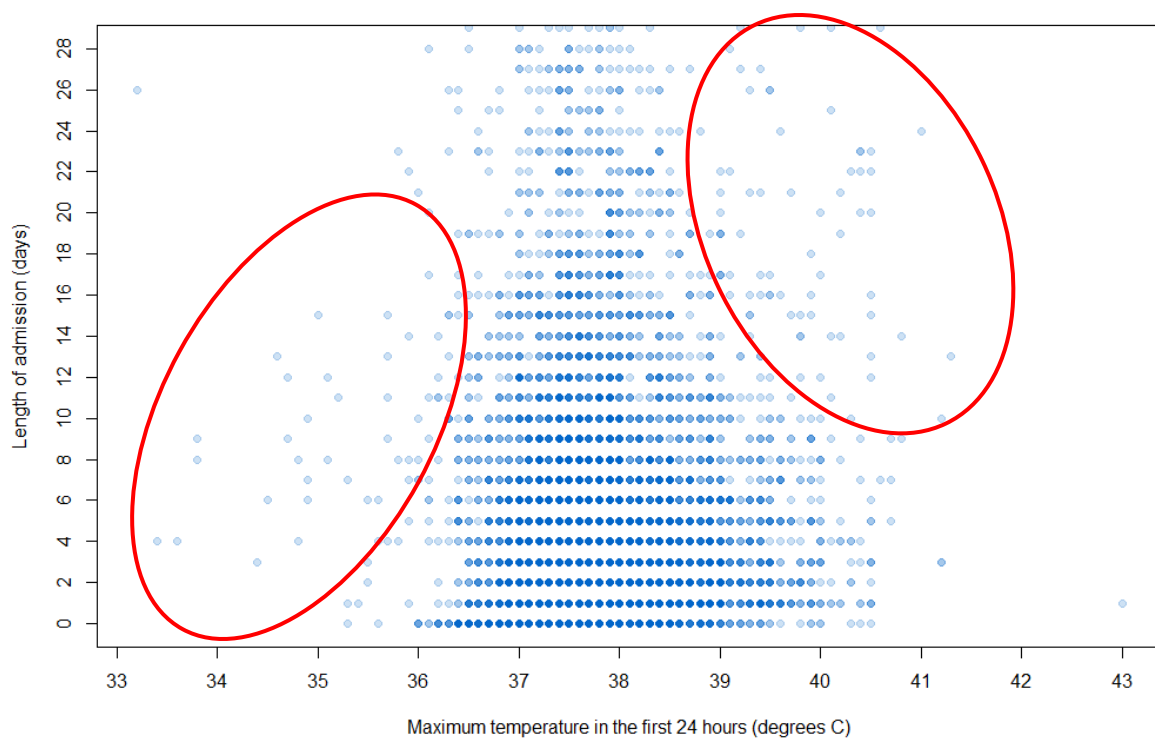


Figure 6.22: Distribution of length of ICU stay for children who survive to ICU discharge, censored at 28 days, according to the maximum temperature in the first 24 hours of admission. Each dot represents a single admission, the colour intensity represents the number of cases with the same maximum temperature and length of stay (intensity increases with frequency). Although there is no strong linear correlation, some patterns can be seen: (1) children with very low maximum temperatures may have comparatively shorter stay than children with very high maximum temperatures (marked by red ellipses), (2) there may be a positive correlation between maximum temperature and length of stay for children admitted <4 days.

6.6 Conclusions

In this chapter, I aimed to explore the association between temperature, specifically maximum temperature in the first 24 hours of admission, and death. This was in line with analysis carried out in a large cohort of adult ICU patients. I also aimed to examine whether the temperature that was associated with the lowest risk of death was context specific. The maximum temperature in the first 24 hours of admission was different amongst survivors and non-survivors in both cohorts. In all populations, having a maximum temperature below 36.5°C were associated with poor outcomes. Once the severity of illness was considered, the optimal temperature was between 37.5-37.9°C in the UK, but 38°C in those with unplanned admissions only. In the FEAST cohort, selected for having suspected infection, the lowest adjusted odds ratio of death was also at a T_{max} of 38°C. In this population the adjusted odds ratio of death was not U-shaped and remained low for temperatures above 38°C. Fever at randomisation did not influence the mortality risk of children who received fluids or not: for both febrile and afebrile subgroups fluid boluses were associated with an increased risk of death. This would suggest that any oxygen debt that may be created by fever may not affect survival, assuming fluid boluses increase oxygen delivery and do not cause harm through any other physiological process.

While these data do not demonstrate a strong beneficial effect of fever, a maximum temperature of 38°C may be associated with some benefit in those with the highest likelihood of infection. This is consistent with adult data and the theoretical benefits of fever seen in vitro on immune function. The ideal temperature may be context specific, although much more work is needed to understand this fully. The analysis does not inform us on whether fever should be treated or not. However, data do suggest that in children with infection and critical illness, fever should not be avoided at all cost. Indeed, there may be benefit in allowing the temperature to rise to >38°C before treating, if at all.

Chapter 7: Conclusions and Future Plans

7.1 Hypothesis testing and concluding statements

The null hypothesis formulated in chapter 1 was that fever does not impact on outcome in critically ill children by affecting the balance between oxygen consumption and delivery. In order to answer this, six questions were posed with experiments and analyses designed to answer these in a population of children admitted to the intensive care units of Great Ormond Street Hospital. These can be summarised as the following:

What is the incidence of fever in children who are admitted to the paediatric intensive care unit? Fever occurs in just under 40% of all children admitted to PICU in the first 48 hours of admission. The incidence is higher (55%) in children with suspected infection. The incidence of fever decreases each day after admission – therefore, fever occurs early in the intensive care unit.

What is the incidence of treatment of fever? Over half the children with fever were treated with anti-pyretic drugs or cooling mechanisms (58% on day 1 of admission). Paracetamol was the commonest anti-pyretic treatment, as over 93% of children with fever received paracetamol. However, paracetamol was widely used irrespective of the presence of fever: from the retrospective data from Great Ormond Street Hospital, 78% of all PICU admissions received paracetamol at some point. Despite this, not all episodes of fever were treated: when considering individual episodes of fever, over half the episodes (57%) were not treated with paracetamol.

What is the effectiveness of treatment of fever? When episodes of fever were treated with paracetamol, the temperature decreased by a mean of 0.78°C by 4 hours after the dose. When episodes of fever were not treated with paracetamol, temperature also

decreased, by a mean of 0.88°C after 4 hours. The temperature was higher and continued for longer in episodes of fever before paracetamol was given, indicating that whether episodes were treated or not may be decided clinically.

What is the change in oxygen consumption and energy expenditure with fever in ICU?

Robust conclusions could not be drawn from the results of the calorimetry measurements due to the small numbers recruited and limitations of the study design. Data from 3 patients available indicated that oxygen consumption may increase between 13 and 34% per 1°C rise in temperature (corresponding to a 12-26% rise in energy consumption). No consistent effect was observed during a decrease in temperature or following paracetamol.

What is the change in cardiac output with fever in ICU? Cardiac output increased by a mean of 10% per 1°C rise in temperature. However, there was a great variability in this relationship between cardiac output and temperature. This was mostly secondary to a rise in heart rate. The relationship between heart rate and temperature was not linear – the rise in heart rate was greatest when the temperature increased between 38 and 39°C. Treatment with paracetamol reduced cardiac output, but this only contributed to a small proportion to the decrease in blood pressure associated with paracetamol (quantified as a 4-6% decrease from baseline).

Is temperature associated with ICU outcomes? A maximum temperature <36.5°C in the first 24-hours of admission was associated with a high risk of mortality in critically ill-children. The optimal temperature associated with survival was 38°C in children following unplanned admission to ICU in the UK, which was higher than those admitted following planned admissions (37.3°C). Higher maximum temperatures ($\geq 40^\circ\text{C}$) were associated with an increase in the risk of mortality (although the risk did not significantly increase more than children with a maximum temperature of 36.5°C), making the relationship between temperature and mortality U-shaped. The optimal temperature was also 38°C in children from the FEAST cohort, although in these children the relative risk of mortality remained low at higher febrile temperatures.

Based on these data, fever, although common, does not show a clear association with poorer outcomes in critically ill children. In children who are more likely to have infection, early fever may be associated with a lower risk of mortality. From the limited data, fever is likely to be associated with an increase in oxygen consumption to a similar extent as previously described in adults. Fever is associated with an increase in oxygen delivery, but may be to a slightly lesser degree than the increase in oxygen consumption i.e. the generation of fever may lead to an oxygen debt. Despite this, those who have a maximum temperature $<36.5^{\circ}\text{C}$ early in critical illness are associated with increased risk of mortality. These children are not subject to the possible oxygen debt from fever. It may be argued that these children are unable spare energy to raise their temperature. In contrast, in those with infection, an oxygen debt incurred by fever may be outweighed by some other benefit, possibly an immune benefit of fever to fight infection.

Therefore, based on the analyses of these data, I accept the null hypothesis: In critically ill children, fever does not impact on critical illness outcomes by significantly affecting oxygen consumption and delivery. It remains possible, that in a small proportion of children, the increase in oxygen consumption required to generate a fever cannot be met by an increase in oxygen delivery. However, this group of children forms a small proportion of the overall PICU population to significantly alter mortality. Even in sub-Saharan populations as represented by those recruited in the FEAST study, mortality was higher in those without fever at randomisation, compared to those with fever. The effect of fever on other outcomes such as length of organ support or long-term organ damage was not explored and warrants further study.

Two central questions led to the formulation of the hypothesis: (i) is fever beneficial or harmful in critically ill children admitted to PICU, and (ii) should fever be treated on PICU? Whilst early fever grade temperatures are associated with a reduced risk of mortality in children with infection, the overall effect of this on mortality is small. Also, any oxygen debt is

small – the increase in oxygen delivery nearly matches the increase in oxygen consumption. On the other hand, fever may confer a small benefit on the immune response. The more important question for clinicians is the one that follows: should fever be treated on PICU? The possible benefit of fever seen in children with infection may be in altering the threshold to use paracetamol, which confers a survival benefit – this would fit Suzuki’s findings [Suzuki 2015]. Based on the argument that fever increases oxygen consumption, treatment of fever may not prevent this: the increase in oxygen consumption is seen during the generation of fever. By the time a child is febrile, an oxygen debt may already have been incurred. Treating ongoing fever may not yield much benefit as (a) the change in temperature over four hours was similar in those treated with paracetamol and those not, and (b) there is some suggestion that after the rise phase, temperature can be maintained through heat conservation (from Barr, Cecil and DuBois’ data and the limited calorimetry data in Chapter 4). A better argument can be made for fever prevention. This is difficult to assess retrospectively, given that 70% of all admissions had paracetamol, the median temperature for children admitted to ICU was around 37°C and 37.6°C was the optimal early maximum temperature associated with survival in the GOSH cohort. It is possible that in many children who did not have a fever, this was prevented by the widespread use of paracetamol. These children with normal body temperature had the best outcomes. Counter to that is the observation that children with maximum body temperatures <36.5°C had relatively worse outcomes. As speculated above, these children may not have had the energy reserves to generate normal or fever grade temperatures, thereby succumbing to their critical illness.

7.2 Future plans

A randomised controlled trial would be the best way to answer the question, whether fever in PICU should be treated or not. Young and colleagues tried to do this in adult ICU in the HEAT trial, comparing the use of paracetamol versus placebo. While there was no difference in outcome, there was also little separation in the mean temperatures between the patients

in the two arms of the trial. A more logical trial would be to compare two different thresholds of treatment of fever. The feasibility of such a trial was tested in the FEVER Feasibility Study [Peters 2019]. The objective of this multi-modal study was to test the feasibility and acceptability of conducting such a trial in PICU: using a proposed restrictive temperature threshold of 37.5°C and a more permissive temperature threshold of 39.5°C. Alongside the observation part of the study described in Chapter 2, a qualitative study and a 4-centre pilot trial was undertaken in 2017. The difference in the mean maximum temperature in the first 48 hours between arms was 0.5°C (95% CI 0.2-0.8°C). There were 2 adverse events in the restrictive arm (seizure and rhabdomyolysis) and 1 in the permissive arm (seizure). Both seizures were deemed by the clinical teams to be unrelated to the trial interventions. These results, and the valuable feedback from parents and clinicians, led to the conclusion that while still feasible, a full trial should be limited to children who were invasively ventilated to reduce the use of paracetamol for comfort. We await to undertake such a trial in the future.

A further question arises from the epidemiological work associating low maximum temperatures with mortality in both PICU and children with infection in sub-Saharan Africa: should children with temperatures <36.5°C, especially those with suspected infection be warmed up, possibly to a fever grade temperature? This may appear logical, especially based on the assumption that fever potentiates the immune response. However, it may be difficult to recommend warming children based on retrospective data: children who were cold may have been actively cooled (for example, those post cardiac arrest in ICU may have had targeted temperature management to prevent fever) or may not be able to generate a fever due to inadequate energy resources (or the inability of oxygen delivery to match the oxygen consumption from fever). It is possible that in this latter group this is an adaptive response, akin to a torporous state – something well described in animals but not so in humans. Intensive care interventions to increase oxygen delivery may harm rather than help recovery in such states. This may support an apparent, albeit non-significant, increase in harm with fluid in febrile children enrolled to FEAST and the harm from higher volume transfusions in

TRACT. Some authors have proposed this as an explanation for why a 'less is more' approach has been supported by most intensive care clinical trials in the last 15 years [Stanzani 2019]. In order to evaluate this hypothesis further, two steps are necessary: (a) patients with hypothermia will need better clinical and biological phenotyping, before (b) a modified treatment approach can be trialled. Such prospective work in children will be difficult given the small numbers of children who are hypothermic and the current inability to study metabolic states in children with minimally invasive techniques. This is highlighted in the difficulty in collecting data on energy consumption in critically ill children with fever. Preliminary work is being done by Prof Mervyn Singer's group at University College London to characterise the mechanisms of thermoregulation in critical illness in adults: this may shed some light on this area in the future [personal communication with Dr Robert Tidswell].

This thesis draws heavily on the use of routinely collected clinical data, some at high-resolution. As a technique, this may be an alternative to laboratory models to understand physiological principles in more detail. Although an estimate of the temperature and heart rate association is made in Chapter 3 using such data, this can be refined using non-linear modelling techniques or even time-series analyses to assess multi-variable dependencies. This can also be extended to more complex physiological principles: for example, by using machine learning techniques to predict fluid responsiveness using heart rate, blood pressure and temperature data at high-resolution. I intend to explore such relationships in the future in collaboration with a multi-disciplinary team of scientists and am currently a co-applicant for a grant from the Engineering and Physical Sciences Research Council (EPSRC) to explore bio-mechanical models in critically ill patients. Knowledge gained from such data sets can then be used prospectively to inform interventional trials. One of the criticisms of randomised controlled trials is that the results are based on an average effect of an intervention on the specific cohort studied. This is necessary: randomised controlled trials must be pragmatic in design for the findings to be applied clinically. This may not consider individuals within the cohort that may benefit from an intervention. This is particularly evident in critical care – most

randomised controlled trials in the last 20 years have shown interventions to be less effective than controls. Clinicians by the bedside may struggle with this when they may have witnessed first-hand a benefit of an intervention in some patients or have a biological basis to believe that the intervention may be beneficial in the patient in front of them. The legacy of FEAST is a good example of this: despite the harm demonstrated from fluids, fluid is still used liberally in sepsis in high income country setting with intensive care provision. The justification for doing so is the belief from clinicians that (a) fluid can cause a demonstrable benefit by the bedside (reduction in heart rate, improvement in perfusion or blood pressure), and (b) the availability of intensive care provisions can mitigate the harmful effects of fluid overload, chloraemia, pulmonary oedema etc. This may be a valid justification – we will not know until this is trialled in the same setting. However, artificial intelligence algorithms applied to patient data collected continuously during routine clinical care can be used in real-time to improve phenotyping of patients. Patients could be randomised to a specific set of interventions based on such real-time physiological data rather than treating broad cohorts (e.g. patients admitted with community acquired pneumonia or sepsis). The randomised treatments can then be compared – this could form the basis of a smart or adaptive trial. Alternatively, competing algorithms could be randomised to decide on the best clinical decision support system.

7.3 Personal reflections

Work within this thesis has been completed over the last 4 years (2015-19). This has allowed me to develop several skills.

- (i) Extraction of routinely collected data: Intensive care units are data rich environments. The use of electronic charting systems and health records allow for bulk extraction of data based on conditional statements. One of the most valuable skills I gained was the ability to do so: although the Philips IntelliSpace

Critical Care and Anaesthesia system had been in use at Great Ormond Street Hospital since 2012, this had not been used as a database from which data was extracted. I gained a lot of insight into the database architecture, learned how to code in SQL and developed previously learnt visual basic programming skills to be able to do this. This is a valuable tool in clinical research, and I have used this in several other research projects in the last 4 years. Of note, work published from exactly such techniques has led to several publications. More importantly, these retrospective observational studies have supported successful funding applications for trials – Oxy-PICU, comparing a conservative versus liberal oxygen saturation target threshold (initially as a feasibility study funded by the Great Ormond Street Hospital Children’s Charity, and subsequently funded for a full trial by the NIHR HTA); PRESSURE, comparing a 5th centile blood pressure threshold in children on vaso-active drugs compared to usual care (funded by the NIHR HTA); and OPTTICCA, a feasibility trial comparing the use of a haemoglobin transfusion threshold of 70 g/L compared to usual care in children on the intensive care unit (funded by the Canadian Institute of Health Research).

- (ii) Use of high-resolution data: Improved data storage and computing ability has opened the door for high-resolution data storage and analysis. As a part of this thesis I used routinely collected high-resolution data from bedside monitors stored using the Etiometry T3 platform. This was a new system installed at Great Ormond Street Hospital for research purposes in 2015. I was the first person to access and use the data to explore the association between temperature and heart rate. This can be developed further as described above, not only to define multi-variable associations, but also to improve phenotyping of individuals using routine monitoring. I have started to explore the use of high-resolution data to augment clinical decision making: in 2019, I took a challenge to the Alan Turing Institute Data Study Group to try and predict the success of extubation in a cohort of over 5000 children admitted to Great Ormond Street Hospital, using machine

learning techniques. As a clinician, this gave me valuable experience in interacting with data scientists to both characterise a problem and understand the application of machine learning to high-resolution data to find solutions to a clinical problem. This is a future direction that I will explore more of and forms the basis of the EPSRC project grant describe above.

- (iii) Patient recruitment to an observational study: The use of indirect calorimetry to measure energy expenditure provided me with valuable experience and insight into prospective clinical research in the paediatric intensive care environment. Even though this was an observational study, recruitment was difficult. Fever occurred early on in patients' admission – this was evident from the epidemiological data in Chapter 2. However, most emergency admissions occurred out of hours, paracetamol was used ubiquitously, the duration of fever was short, and children were often unstable in early this period (optimisation of ventilation, high oxygen requirements, need for airway clearance, use of high-pressure ventilation). Parents were often anxious and the introduction of yet another machine, one that would not benefit their child, was often a barrier to consent for participation. Consenting parents in such stressful contexts requires a great degree of skill – this work has helped me appreciate this more and helped me with the language and approach used for research consent. It has also demonstrated to me the importance of research without prior consent in trials testing routinely used interventions – informed consent would be very difficult to achieve in most circumstances, especially when randomisation must happen early in the child's intensive care admission. This model of deferred consent has been used in most recent trials in PICU and remains the most effective way of conducting meaningful and inclusive clinical research in this environment.
- (iv) Experience in working with a Clinical Trials Unit: This thesis was written in the context of the application for funding and subsequent conduct of the Fever Feasibility Study (funded by the NIHR HTA). Some of the early epidemiological

work informed the feasibility study design, as part of the Observational Study questionnaire. In doing so, I have managed to participate and observe at close quarters the planning and organisation involved in the set-up of a study, including a multi-centre randomised controlled trial. Being able to work with the Clinical Trials Unit at the Intensive Care National Audit and Research Centre (ICNARC) was hugely educational. This has led to strong links being formed and I have subsequently been a co-applicant for funding for both Oxy-PICU (funded by NIHR HTA, due to start recruitment in early 2020) and PRESSURE (funded by NIHR HTA, due to start recruitment in late 2020).

The knowledge and research skills developed during the process of the research degree have been invaluable. I believe they will hold me in good stead in the future to develop a career in clinical academia in the critical care environment.

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Appendix A

Steps taken to analyse retrospective temperature data from Great Ormond Street Hospital ICUs

1. *Data extracted from the Philips IntelliSpace Critical Care and Anaesthesia using Microsoft SQL Server using following code*

```
Select distinct en.lifeTimeNumber, en.encounterId, pass.chartTime,
intv.shortLabel, pass.verboseForm, att.shortLabel, pass.valueNumber, cen.inTime
From dbo.PtAssessment as pass, dbo.D_Encounter as en, dbo.D_Intervention as
intv, dbo.PtCensus as cen, dbo.D_Attribute as att
Where en.encounterId=pass.encounterId and att.attributeId=pass.attributeId and
intv.interventionId=pass.interventionId and
intv.shortLabel IN ('Temp. 1', 'Temp. 2', 'Temp. 3') and
pass.chartTime<DATEADD(DAY,3,cen.inTime) and
cen.encounterId=pass.encounterId and att.shortLabel in ('Temp', 'Site') AND
cen.inTime BETWEEN '2012-04-01 00:00' AND '2017-12-31 23:59';
```

2. *Data included site of measurement and temperature values. Site of temperature measurement matched to value using time of measurement, label and patient identifier in Microsoft Excel using visual basic*

```
Sub sitematch()
```

```
Dim i, j As Single 'nested loops used to match temperature site and value
```

```
i = 2
```

```
For i = 2 To 238434
```

```
    j = 2
```

```
    For j = 2 To 242014 'if patient identifier, site and time matched
```

```
        If Cells(i, 13).Value = Cells(j, 1).Value And Cells(i, 15).Value = Cells(j,
3).Value And Cells(i, 16).Value = Cells(j, 4).Value Then
```

```
            Cells(j, 9).Value = Cells(i, 17).Value
```

```
        j = 242014
```

```
    End If
```

```
Next j
```

```
Next i
```

```
End Sub
```

3. Only temperature values labelled 'core', 'oesophageal', 'rectal', 'bladder', 'axillary' or 'tympanic' considered. Admission time assigned as submitted to PICANET database (rather than as used in ICCA to match outcomes)

4. These were sorted in relation to admission time, as submitted to the PICANET database using the following visual basic code (batched according to year of admission)

```
Sub profiler()
```

```
Dim i, j, hour, n As Single
```

```
i = 107281
```

```
For i = 107281 To 109027
```

```
    j = 2
```

```
    For j = 2 To 107263
```

```
        hour = 0
```

```
        If Cells(i, 1).Value = Cells(j, 1).Value Then hour =
```

```
WorksheetFunction.RoundUp(((Cells(j, 3).Value - Cells(i, 2).Value) *  
24), 0)
```

```
        If hour >= 1 And hour <= 48 Then
```

```
            If Cells(i, 5 + hour).Value = "" Or Cells(i, 5 + hour).Value <  
Cells(j, 7).Value Then Cells(i, 5 + hour).Value = Cells(j,  
7).Value
```

```
        End If
```

```
    Next j
```

```
Next i
```

```
End Sub
```

5. Summary statistics calculated for each hour for the first 48 hours using the following r code

#converting hourly temperature data from columns to rows

```
id=rep(temp$patientid,48)
```

```
h=c()
```

```
for (i in 1:48){h=c(h, rep(i, 10379))}
```

```
t=c()
```

```
t=c(temp$h1,temp$h2,temp$h3,temp$h4,temp$h5,temp$h6,temp$h7,temp$h8,temp  
$h9,temp$h10,temp$h11,temp$h12,temp$h13,temp$h14,temp$h15,temp$h16,temp  
$h17,temp$h18,temp$h19,temp$h20,temp$h21,temp$h22,temp$h23,temp$h24,tem  
p$h25,temp$h26,temp$h27,temp$h28,temp$h29,temp$h30,temp$h31,temp$h32,te  
mp$h33,temp$h34,temp$h35,temp$h36,temp$h37,temp$h38,temp$h39,temp$h40,t  
emp$h41,temp$h42,temp$h43,temp$h44,temp$h45,temp$h46,temp$h47,temp$h48)
```

```
#temperatures below 32°C removed
```

```
t32=c()
```

```
t32=t
```

```
t32[t<32]=NA
```

```
#median temperature for each hour calculated
```

```
tmed=c()
```

```
for (i in 1:48){tmed=c(tmed,median(na.omit(t32[h==i])))}
```

```
#5th, 25th, 75th and 95th centile temperatures for each hour calculated
```

```
tq25=c()
```

```
for (i in 1:48){tq25=c(tq25,quantile(na.omit(t32[h==i]),0.25))}
```

```
tq75=c()
```

```
for (i in 1:48){tq75=c(tq75,quantile(na.omit(t32[h==i]),0.75))}
```

```
tq05=c()
```

```
for (i in 1:48){tq05=c(tq05,quantile(na.omit(t32[h==i]),0.05))}
```

```
tq95=c()
```

```
for (i in 1:48){tq95=c(tq95,quantile(na.omit(t32[h==i]),0.95))}
```

6. *Data plotted to demonstrate distributions using following r code*

```
plot(tmed~c(1:48),type="l",ylim=c(34,40),lwd=2,col="blue",xaxt="n",xlab="Hours form admission",ylab="Temperature (degrees Celsius)")
```

```
polygon(c(1:48,48:1),c(tq25,rev(tq75)),col=rgb(0,100,200,max=255,alpha=100),border=FALSE)
```

```
polygon(c(1:48,48:1),c(tq05,rev(tq95)),col=rgb(0,50,250,max=255,alpha=50),border=FALSE)
```

```
axis(1,at=c(1:48),labels=c(1:48),cex.axis=0.7)
```

```
abline(h=37,lty=2,col="gray50")
```

```
abline(h=38,lty=2,col="gray50")
```

7. *Hour of first fever calculated in r*

```
fhour=c()
```

```
for (i in 1:10379){fhour=c(fhour,min(h[t>=38 & adno==i],na.rm=TRUE))}
```

8. *Time-to-event curves for fever created using following r code and the survival package*

```
fever=temp$fever #binary variable indicating whether fever temperature >38°C in first 48 hours or not
```

```
fever=as.factor(temp$fever)
```

```
fhour[temp$fever==0]=49 #right censoring admissions with no fever
```

```
timeobj=Surv(fhour,fever)
```

```
kmobj=survfit(timeobj~1)
```

```
plot(kmobj,ylim=c(0,1),xlim=c(1,48),col="blue",xaxt="n",xlab="Hours from admission
to PICU",ylab="Probability of developing fever")
axis(1,at=c(0:48),labels=c(0:48))
```

9. *Histograms of first and final hours of fever in the first 48 hours*

```
#First hour of fever for each patient
```

```
fhour=c()
for (i in 1:10379){fhour=c(fhour,min(h[t>=38 & adno==i],na.rm=TRUE))}
```

```
#Number of children with first fever in each hour for the first 48 hours
```

```
fhourna=c()
for (i in 1:48){fhourna=c(fhourna,length(na.omit(fhour[fhour==i])))}
barplot(fhourna,width=1,space=0,ylim=c(0,500),col="skyblue",xlab="Hours from
admission to PICU",ylab="Frequency")
axis(1,at=seq(0.5,47.5),labels=c(1:48),cex.axis=0.7)
```

```
#Final hour of fever for each patient
```

```
fmaxhour=c()
for (i in 1:10379){fmaxhour=c(fmaxhour,max(h[t>=38 & adno==i],na.rm=TRUE))}
```

```
#Number of children with final fever in each hour for the first 48 hours
```

```
fmaxhourna=c()
for (i in 1:48){fmaxhourna=c(fmaxhourna,length(na.omit(fmaxhour[fmaxhour==i])))}
fmaxhourna
barplot(fmaxhourna,width=1,space=0,ylim=c(0,500),col="skyblue",xlab="Hours from
admission to PICU",ylab="Frequency")
axis(1,at=seq(0.5,47.5),labels=c(1:48),cex.axis=0.7)
```

10. *Histogram and density plots of number of fever grade temperature measurements*

```
#number of fever grade temperatures per hour
```

```
fsumhour=c()
for (i in 1:10379){fsumhour=c(fsumhour,sum(!is.na(h[t>=38 & adno==i])))}
summary(fsumhour)
```

```
#histogram of number of fever grade temperatures per hour in the first 48 hours
```

```
fsumhourna=c()
for (i in 1:48){fsumhourna=c(fsumhourna,length(na.omit(fsumhour[fsumhour==i])))}
fsumhourna
barplot(fsumhourna,width=1,space=0,ylim=c(0,1500),col="skyblue",xlab="Hours from
admission to PICU",ylab="Frequency")
axis(1,at=seq(0.5,47.5),labels=c(1:48),cex.axis=0.7)
```

```
#total number of temperatures recorded per hour
```

```
tsumhour=c()
```

```

for (i in 1:10379){tsumhour=c(tsumhour,sum(!is.na(h[t32>0 & adno==i])))}
summary(tsumhour)
#fraction of fever grade temperatures per hour of total number of measurements
sumfrac=c()
sumfrac=fsumhour/tsumhour*100
plot(density(na.omit(sumfrac)),lwd=2,col="blue",main="",xlab="% of temperature
measurements >=38 degrees C")

hfev=h[fever==1] #hour values for children with fever in first 48 hours only
t32fev=t32[fever==1] #temperature values of those with fever in first 48 hours only
adnofev=adno[fever==1] #admission number of those with fever in first 48 hours only
tsumhourfev=c()
for (i in 1:10379){tsumhourfev=c(tsumhourfev,sum(!is.na(hfev[t32fev>0 &
adnofev==i])))}
summary(tsumhourfev)
fsumhourfev=c()
for (i in 1:10379){fsumhourfev=c(fsumhourfev,sum(!is.na(hfev[t32fev>=38 &
adnofev==i])))}
summary(fsumhourfev)
feverfrac=c()
feverfrac=fsumhourfev/tsumhourfev*100
summary(feverfrac)
plot(density(na.omit(feverfrac)),lwd=2,col="blue",main="",xlab="% of temperature
measurements >=38 degrees C")

```

Steps taken to analyse prospective observational data from Great Ormond Street Hospital collected as part of the Fever Observational Study

1. Data submitted to PICANET portal for the Fever Observational Study read into variable fos in r

```

#children who fulfilled exclusion criteria assigned excl==1
excl=c()
excl=rep(0,273)
excl[fos$DeathImminent==1]=1
excl[fos$CardioPulmonaryBypass==1]=1
excl[fos$AdWithMyocardialDisease==1]=1

```

```

excl[fos$AdWithMalignantHyperthermia==1]=1
excl[fos$AdWithDrugInducedHyperthermia==1]=1
excl[fos$AdWithAcuteEncephalopathy==1]=1
excl[fos$AdWithNeurolepticMalignantSyndrome==1]=1
excl[fos$AdWithSevereRhabdomyolysis==1]=1
#children with infection known or suspected assigned inf==1
inf=rep(0,273)
inf[fos$AdmissionInfection==1]=1
inf[fos$AdmissionInfection==2]=1
#eligible patients assigned eligible==1
eligible=rep(0,273)
eligible[excl==0 & inf==1]=1
#maximum temperature for each day assigned to separate variables
adtemp=fos$TemperatureFirstContact[eligible==1]
adtemp[adtemp==99]=NA
d0temp=fos$HighestTemperatureDay0[eligible==1]
d0temp[d0temp==99]=NA
d1temp=fos$HighestTemperatureDay1[eligible==1]
d1temp[d1temp==99]=NA
d2temp=fos$HighestTemperatureDay2[eligible==1]
d2temp[d2temp==99]=NA
d3temp=fos$HighestTemperatureDay3[eligible==1]
d3temp[d3temp==99]=NA
d4temp=fos$HighestTemperatureDay4[eligible==1]
d4temp[d4temp==99]=NA
#day and temperature data aggregated
day=c(rep(0,140),rep(1,140),rep(2,140),rep(3,140),rep(4,140))
day=as.factor(day)
temp=c(d0temp,d1temp,d2temp,d3temp,d4temp)

```

2. *Beanplots of maximum temperature data per calendar day plotted using beanplot package*

```

beanplot(temp~day,col="skyblue",xlab="Days of admission",ylab="Maximum
temperature (degrees C)")
abline(h=38,lty=2,lwd=2,col="red")

```
3. *Barplots showing proportion of children with fever for each calendar day*

```

fever=rep(0,700)
fever[temp>=38]=1

```

```
barplot(table(fever,day),ylim=c(0,140),col=c("darkblue","red"),xlab="Day of PICU admission",ylab="Frequency")
```

4. *Cumulative distributions below and above the maximum temperatures when fever is treated plotted*

```
#use of paracetamol per calendar day assigned
```

```
d0para=fos$ParacetamolDay0[eligible==1]
```

```
d1para=fos$ParacetamolDay1[eligible==1]
```

```
d2para=fos$ParacetamolDay2[eligible==1]
```

```
d3para=fos$ParacetamolDay3[eligible==1]
```

```
d4para=fos$ParacetamolDay4[eligible==1]
```

```
d0cool=d0para
```

```
d1cool=d1para
```

```
d2cool=d2para
```

```
d3cool=d3para
```

```
d4cool=d4para
```

```
para=c(d0para,d1para,d2para,d3para,d4para)
```

```
#use of other anti-pyretic interventions assigned
```

```
d0cool[fos$NsaidDay0[eligible==1]==1]=1
```

```
d0cool[fos$ExternalCoolingDay0[eligible==1]==1]=1
```

```
d0cool[fos$OtherCoolingDay0[eligible==1]==1]=1
```

```
d1cool[fos$NsaidDay1[eligible==1]==1]=1
```

```
d1cool[fos$ExternalCoolingDay1[eligible==1]==1]=1
```

```
d1cool[fos$OtherCoolingDay1[eligible==1]==1]=1
```

```
d2cool[fos$NsaidDay2[eligible==1]==1]=1
```

```
d2cool[fos$ExternalCoolingDay2[eligible==1]==1]=1
```

```
d2cool[fos$OtherCoolingDay2[eligible==1]==1]=1
```

```
d3cool[fos$NsaidDay3[eligible==1]==1]=1
```

```
d3cool[fos$ExternalCoolingDay3[eligible==1]==1]=1
```

```
d3cool[fos$OtherCoolingDay3[eligible==1]==1]=1
```

```
d4cool[fos$NsaidDay4[eligible==1]==1]=1
```

```
d4cool[fos$ExternalCoolingDay4[eligible==1]==1]=1
```

```
d4cool[fos$OtherCoolingDay4[eligible==1]==1]=1
```

```
cool=c(d0cool,d1cool,d2cool,d3cool,d4cool)
```

```
#cumulative distribution below each temperature for which anti-pyretic intervention used calculated
```

```
lcumcool=c()
```

```
for (i in 0:60)
```



```

      {lcumcool=c(lcumcool,sum(cool[is.na(temp)==0 &
      temp<(35+(i/10)])*100/length(temp[is.na(temp)==0 & temp<(35+(i/10)])))]}
#cumulative distribution above each temperature for which anti-pyretic intervention
used calculated
gcumcool=c()
for (i in 0:60)
  {gcumcool=c(gcumcool,sum(cool[is.na(temp)==0 &
  temp>(35+(i/10)])*100/length(temp[is.na(temp)==0 & temp>(35+(i/10)])))]}

plot((lcumcool)~seq(35,41,0.1),type="l",lwd=2,ylim=c(0,100),xlim=c(36.0,39.5),xlab="
Maximum temperature (degrees C)", ylab="Percentage of patients above and
beyond temperature threshold receiving any antipyretic intervention",
col="forestgreen")
lines(gcumcool~seq(35,41,0.1),col="blue",lwd=2)

```

5. *Cumulative distributions of temperature on the day of first anti-pyretic intervention use and day prior*

```

#temperatures on day of first anti-pyretic intervention, excluding those who had anti-
pyretic intervention on day 0
paraday=c()
paraday=c(d1temp[d0cool==0 & d1cool==1], d2temp[d0cool==0 & d1cool==0 &
d2cool==1],d3temp[d0cool==0 & d1cool==0 & d2cool==0 & d3cool==1],
d4temp[d0cool==0 & d1cool==0 & d2cool==0 & d3cool==0 & d4cool==1])
#temperatures on the day prior to first day of anti-pyretic use
priorday=c()
priorday=c(d0temp[d0cool==0 & d1cool==1], d1temp[d0cool==0 & d1cool==0 &
d2cool==1],d2temp[d0cool==0 & d1cool==0 & d2cool==0 & d3cool==1],
d3temp[d0cool==0 & d1cool==0 & d2cool==0 & d3cool==0 & d4cool==1])
#cumulative distribution of temperatures above each temperature threshold for anti-
pyretic intervention
paradist=c()
for (i in 0:60){paradist=c(paradist,sum(paraday<(35+i/10)))}
priordist=c()
for (i in 0:60){priordist=c(priordist,sum(priorday<(35+i/10)))}
plot(paradist*100/52~seq(35,41,0.1),type="l",lwd=2,col="forestgreen",xlab="Maximu
m temperature (degrees C)",ylab="Cumulative percentage of patients")
lines(priordist*100/51~seq(35,41,0.1),lwd=2,col="blue")

```

Steps taken to analyse the temperature change post paracetamol and fever treated without paracetamol

1. *Data on paracetamol doses downloaded from Philips IntelliSpace Critical Care And Anaesthesia Electronic Health Record database using the following SQL code*

```
Select distinct en.lifeTimeNumber, en.episodeId, intv.shortLabel, meds.chartTime,
meds.valueNumber, meds.unitOfMeasure, cen.inTime
From dbo.PtMedication as meds, dbo.PtAssessment as pass, dbo.D_Encounter as en,
dbo.D_Intervention as intv, dbo.D_Site as mode, dbo.PtCensus as cen
Where (cen.inTime between '2012-04-01 00:00:00.00' and '2016-12-31
23:59:59.99') and intv.shortLabel LIKE '%PARACETAMOL%' and
en.encounterId=meds.encounterId and intv.interventionId=meds.interventionId and
cen.encounterId=en.encounterId and meds.valueNumber<>0;
```

2. *Temperature data downloaded from the same database for patients who had paracetamol (selected by hospital number) using the following SQL query*

```
Select distinct en.lifeTimeNumber, en.episodeId, pass.chartTime,
intv.shortLabel, pass.verboseForm, att.shortLabel, pass.valueNumber
From dbo.PtAssessment as pass, dbo.D_Attribute as att, dbo.D_Encounter as en,
dbo.D_Intervention as intv, dbo.PtCensus as cen
Where en.lifeTimeNumber IN('xxxxxx',...)
and en.encounterId=pass.encounterId and att.attributeId=pass.attributeId and
intv.interventionId=pass.interventionId and intv.shortLabel IN ('Temp. 1',
'Temp. 2', 'Temp. 3') and
pass.chartTime>=cen.inTime and cen.encounterId=pass.encounterId and
att.shortLabel in ('Temp', 'Site');
```

3. *Temperature data matched to paracetamol dose according to time of dose and temperature measurement using visual basic in Microsoft Excel*

```
Sub timematch()
```

```
Dim i, j As Single
```

```
i = 2
```

```
For i = 2 To 21806
```

```
    j = 2
```

```
    For j = 2 To 170204
```

```
        'temperature measurement taken an hour before paracetamol
```

```
If Cells(i, 13).Value = Cells(j, 1).Value And Cells(i, 16).Value - Cells(j, 3).Value <= 0.0625 And Cells(i, 16).Value - Cells(j, 3).Value > 0.02083333 Then
    Cells(i, 23).Value = Cells(j, 7).Value
    Cells(i, 24).Value = Cells(j, 8).Value
```

```
End If
```

'temperature measurement taken in the hour of paracetamol dose

```
If Cells(i, 13).Value = Cells(j, 1).Value And Cells(i, 16).Value - Cells(j, 3).Value <= 0.02083333 And Cells(i, 16).Value - Cells(j, 3).Value > - 0.02083333 Then
```

```
    Cells(i, 25).Value = Cells(j, 7).Value
    Cells(i, 26).Value = Cells(j, 8).Value
```

```
End If
```

'temperature measurement taken in the hour after paracetamol

```
If Cells(i, 13).Value = Cells(j, 1).Value And Cells(j, 3).Value - Cells(i, 16).Value > 0.02083333 And Cells(j, 3).Value - Cells(i, 16).Value <= 0.0625 Then
```

```
    Cells(i, 27).Value = Cells(j, 7).Value
    Cells(i, 28).Value = Cells(j, 8).Value
```

```
End If
```

'temperature measurement taken 2 hours after paracetamol

```
If Cells(i, 13).Value = Cells(j, 1).Value And Cells(j, 3).Value - Cells(i, 16).Value > 0.0625 And Cells(j, 3).Value - Cells(i, 16).Value <= 0.10416667 Then
```

```
    Cells(i, 29).Value = Cells(j, 7).Value
    Cells(i, 30).Value = Cells(j, 8).Value
```

```
End If
```

'temperature measurement taken 3 hours after paracetamol

```
If Cells(i, 13).Value = Cells(j, 1).Value And Cells(j, 3).Value - Cells(i, 16).Value > 0.10416667 And Cells(j, 3).Value - Cells(i, 16).Value <= 0.14583333 Then
```

```
    Cells(i, 31).Value = Cells(j, 7).Value
    Cells(i, 32).Value = Cells(j, 8).Value
```

```
End If
```

'temperature measurement taken 4 hours after paracetamol

```

        If Cells(i, 13).Value = Cells(j, 1).Value And Cells(j, 3).Value - Cells(i,
        16).Value > 0.14583333 And Cells(j, 3).Value - Cells(i, 16).Value <=
        0.1875 Then
            Cells(i, 33).Value = Cells(j, 7).Value
            Cells(i, 34).Value = Cells(j, 8).Value
        End If
    Next j
Next i
End Sub

```

4. *Variables regarding unit and admission weight taken from unit data submitted to PICANET. Data matched according to patient hospital number and paracetamol dose time in Microsoft Excel using visual basic*
5. *Data for children with fever downloaded from Philips IntelliSpace Critical Care And Anaesthesia Electronic Health Record database using following SQL query*

```

Select distinct en.lifeTimeNumber, en.episodeId, pass.chartTime,
intv.shortLabel, pass.verboseForm, att.shortLabel, pass.valueNumber
From dbo.PtAssessment as pass, dbo.D_Attribute as att, dbo.D_Encounter as en,
dbo.D_Intervention as intv, dbo.PtCensus as cen
Where en.lifeTimeNumber IN ('xxxxxx',...) and en.encounterId=pass.encounterId
and att.attributeId=pass.attributeId
and intv.interventionId=pass.interventionId and intv.shortLabel IN ('Temp. 1',
'Temp. 2', 'Temp. 3')
and pass.chartTime>=cen.inTime and cen.encounterId=pass.encounterId and
att.shortLabel in ('Temp', 'Site')
and (pass.valueNumber>=38 or att.shortLabel='Site');

```

Hospital numbers 'xxxxxx' chosen according data submitted to PICANET for children admitted to the individual ICUs for the period of study.

6. *Data for children with fever without paracetamol matched in Microsoft Excel using the following visual basic code*

```

Sub timematch()
Dim i, j As Single
i = 700
For i = 700 To 1419
j = 2

```

For j = 2 To 102346

'temperature measurement taken in the hour before fever without
paracetamol

If Cells(i, 13).Value = Cells(j, 1).Value And Cells(i, 15).Value - Cells(j,
3).Value <= 0.0625 And Cells(i, 15).Value - Cells(j, 3).Value >

0.02083333 Then

Cells(i, 23).Value = Cells(j, 7).Value

Cells(i, 24).Value = Cells(j, 8).Value

End If

'temperature measurement taken in the hour of fever without
paracetamol

If Cells(i, 13).Value = Cells(j, 1).Value And Cells(i, 16).Value - Cells(j,
3).Value <= 0.0208333 And Cells(i, 16).Value - Cells(j, 3).Value > -

0.02083333 Then

Cells(i, 25).Value = Cells(j, 7).Value

Cells(i, 26).Value = Cells(j, 8).Value

End If

'temperature measurement taken in the hour after fever without
paracetamol

If Cells(i, 13).Value = Cells(j, 1).Value And Cells(j, 3).Value - Cells(i,
15).Value > 0.0208333 And Cells(j, 3).Value - Cells(i, 15).Value <=

0.0625 Then

Cells(i, 27).Value = Cells(j, 7).Value

Cells(i, 28).Value = Cells(j, 8).Value

End If

'temperature measurement taken 2 hours after fever without
paracetamol

If Cells(i, 13).Value = Cells(j, 1).Value And Cells(j, 3).Value - Cells(i,
15).Value > 0.0625 And Cells(j, 3).Value - Cells(i, 15).Value <=

0.10416667 Then

Cells(i, 29).Value = Cells(j, 7).Value

Cells(i, 30).Value = Cells(j, 8).Value

End If

'temperature measurement taken 3 hours after fever without
paracetamol

```
If Cells(i, 13).Value = Cells(j, 1).Value And Cells(j, 3).Value - Cells(i,
15).Value > 0.10416667 And Cells(j, 3).Value - Cells(i, 15).Value <=
0.14583333 Then
```

```
    Cells(i, 31).Value = Cells(j, 7).Value
```

```
    Cells(i, 32).Value = Cells(j, 8).Value
```

```
End If
```

```
'temperature measurement taken 4 hours after fever without
paracetamol
```

```
If Cells(i, 13).Value = Cells(j, 1).Value And Cells(j, 3).Value - Cells(i,
15).Value > 0.14583333 And Cells(j, 3).Value - Cells(i, 15).Value <=
0.1875 Then
```

```
    Cells(i, 33).Value = Cells(j, 7).Value
```

```
    Cells(i, 34).Value = Cells(j, 8).Value
```

```
End If
```

```
Next j
```

```
Next i
```

```
End Sub
```

7. *Data read into r. Temperature changes for each time-point in relation to paracetamol dose analysed using a multi-level model using the lme4 package in r*

```
#data stored in rtemp assigned individual variables
```

```
id=rtemp$id
```

```
tp=as.factor(rtemp$timepoint)
```

```
temp=rtemp$temperature
```

```
dose=rtemp$dose
```

```
route=rtemp$route
```

```
fever=rtemp$fever38
```

```
unit=rtemp$unit
```

```
pim=rtemp$pim
```

```
para=as.factor(rtemp$para)
```

```
weight=rtemp$weight
```

```
dpw=rtemp$dosepweight
```

```
doseno=rtemp$doseno
```

```
#variables when paracetamol was given (group P)
```

```
temp.para=temp[para==1]
```

```
id.para=id[para==1]
```

```
tp.para=tp[para==1]
```

```
pim.para=pim[para==1]
```

```

weight.para=weight[para==1]
doseno.para=doseno[para==1]
dpw.para=dpw[para==1]
#variables when paracetamol was given and fever at baseline (group P|F)
temp.paraF=temp.para[fever==1]
tp.paraF=tp.para[fever==1]
weight.paraF=weight.para[fever==1]
pim.paraF=pim.para[fever==1]
id.paraF=id.para[fever==1]
doseno.paraF=doseno.para[fever==1]
dpw.paraF=dpw.para[fever==1]
#model analysing temperature change according to time-point in relation to paraceta
mol dose
fit.para=lmer(temp.para~tp.para+weight.para+pim.para-
1+(1|id.para)+(1|doseno.para))
#model analysing temperature change according to time-point in relation to paraceta
mol dose when fever present at baseline
fit.paraF=lmer(temp.paraF~tp.paraF+weight.paraF+pim.paraF-
1+(1|id.paraF)+(1|doseno.paraF))
8. Exploring effect of dose per weight of paracetamol used by comparing nested models
with and without a dose per weight interaction term
#model analysing temperature change according to time-point in relation to paraceta
mol dose with a dose per weight interaction term
fit.para2=lmer(temp.para~tp.para*dpw.para+weight.para+pim.para-1+(1|id.para)+(1|d
oseno.para))
#comparison of nested models using the likelihood ratio test
anova(fit.para,fit.para2,test="chisq")
9. Exploring the change in temperature in the group with fever who did not receive
paracetamol in the previous 6 hours
#variables when paracetamol was given and fever at baseline (group P|F)
temp.nopara=temp[para==0]
id.nopara=id[para==0]
tp.nopara=tp[para==0]
doseno.nopara=doseno[para==0]
weight.nopara=weight[para==0]
pim.nopara=pim[para==0]

```

```
#model analysing temperature change according to time-point in following fever when no paracetamol given
```

```
fit.nopara=lmer(temp.nopara~tp.nopara+weight.nopara+pim.nopara-1+(1|id.nopara)+(1|doseno.nopara))
```

10. Comparing changes of temperature in fever when paracetamol given (group P|F) and not (group F)

```
#variables when fever present at baseline
```

```
temp.fever=temp[fever==1]
```

```
id.fever=id[fever==1]
```

```
tp.fever=tp[fever==1]
```

```
doseno.fever=doseno[fever==1]
```

```
weight.fever=weight[fever==1]
```

```
pim.fever=pim[fever==1]
```

```
#model for analysing temperature change in all children with fever
```

```
fit.fever=lmer(temp.fever~tp.fever-1+weight.fever+pim.fever+(1|id.fever)+(1|doseno.fever))
```

```
#model for analysing temperature change in children with fever with whether paracetamol given or not as a binary interaction term
```

```
fit.pf=lmer(temp.fever~tp.fever*para.fever+weight.fever+pim.fever+(1|id.fever)+(1|doseno.fever))
```

```
#comparison of nested models
```

```
anova(fit.fever,fit.pf,test="chisq")
```


Appendix B

Fever Observational Study Case Report Form. The form was designed by the Intensive Care National Audit and Research Centre as the Clinical Trials Unit. I was part of the study group that determined the content in the form.



Case Report Form

Your PICU is participating in the Fever Observational Study

Please complete this booklet for all unplanned admissions

Identifiers

Identifiers are for site use only

PICANet event ID

--	--	--	--	--	--	--	--	--	--

Case note number

--	--	--	--	--	--	--	--	--	--

Date/Time of admission to PICU

Date:

D	D
---	---

 /

M	M
---	---

 /

2	0	1	Y
---	---	---	---

 Time:

H	H
---	---

 :

M	M
---	---

 (24-hour clock)

Stage 1

On admission, was an end-of-life care plan in place or was death perceived as imminent?
(Death perceived as imminent – patient was not expected to survive PICU stay)

Yes	<input type="radio"/>	No	<input type="radio"/>
-----	-----------------------	----	-----------------------

Was the patient admitted to ICU following cardiopulmonary bypass?

Yes	<input type="radio"/>	No	<input type="radio"/>
-----	-----------------------	----	-----------------------

On admission, did the patient have any of the following?

Myocardial disease

Yes	<input type="radio"/>	No	<input type="radio"/>
-----	-----------------------	----	-----------------------

Acute encephalopathy
(Including convulsive status epilepticus)

Yes	<input type="radio"/>	No	<input type="radio"/>
-----	-----------------------	----	-----------------------

Malignant hyperthermia

Yes	<input type="radio"/>	No	<input type="radio"/>
-----	-----------------------	----	-----------------------

Neuroleptic malignant syndrome

Yes	<input type="radio"/>	No	<input type="radio"/>
-----	-----------------------	----	-----------------------

Drug-induced hyperthermia

Yes	<input type="radio"/>	No	<input type="radio"/>
-----	-----------------------	----	-----------------------

Severe rhabdomyolysis

Yes	<input type="radio"/>	No	<input type="radio"/>
-----	-----------------------	----	-----------------------

If any are ticked 'yes', then stop here

Stage 2

On admission, did the patient have an infection?
(Includes bacterial, viral and fungal infections)

Confirmed infection

Suspected infection

No infection

If patient does not have a confirmed or suspected infection, then stop here



Infection

Site of infection – provide best available information from PICU stay. If infection was confirmed during PICU stay, select the origin of the sample in which the primary organism causing the infection was confirmed. If infection was suspected but not confirmed during PICU stay, select the site(s) where infection was suspected.

Type of infection – for infections confirmed at admission or suspected infections that are later confirmed during PICU stay, indicate the primary organism causing the infection.

Temperature

Temperature at first face-to-face contact – the first temperature taken after first face-to-face contact with PICU or retrieval staff.

Daily data

Day 0 – first day in PICU from admission until 23:59.

NSAID – tick 'yes' if the patient has received non-steroidal anti-inflammatory drugs.

External cooling – tick 'yes' if any external interventions were used with the aim of reducing the patient's temperature, such as a cooling blanket, sponging, cold bath, ice packs or fans.

Other cooling – tick 'yes' if any other interventions were given with the aim of reducing the patient's temperature, such as chilled intravenous (IV) fluids, chilled peritoneal dialysis (PD) fluids or cooling on extra-corporeal circuit.



Stage 3

Infection

Site of infection

Lungs	<input type="radio"/> L	Soft tissue	<input type="radio"/> S	Central nervous system	<input type="radio"/> C
Blood	<input type="radio"/> B	Abdomen	<input type="radio"/> A	Urinary tract	<input type="radio"/> U
Other	<input type="radio"/> O	Please specify: <input type="text"/>			

Type of infection (only for infections confirmed during PICU stay)

Virus	<input type="radio"/> V	
Bacteria	<input type="radio"/> B	
Other	<input type="radio"/> O	Please specify: <input type="text"/>

Temperature

Temperature at first face-to-face contact:
(with PICU or retrieval staff)

<input type="text"/>	<input type="text"/>	.	<input type="text"/>	°C
----------------------	----------------------	---	----------------------	----

Daily data

Day 0 = first day in PICU from admission until 23:59. Subsequent days are from 00:00 – 23:59.
Complete for each day of PICU stay, up to and including day 4.

	Day 0		Day 1		Day 2		Day 3		Day 4	
Highest temperature (°C)	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Paracetamol	Yes <input type="radio"/> Y	No <input type="radio"/> N	Yes <input type="radio"/> Y	No <input type="radio"/> N	Yes <input type="radio"/> Y	No <input type="radio"/> N	Yes <input type="radio"/> Y	No <input type="radio"/> N	Yes <input type="radio"/> Y	No <input type="radio"/> N
NSAID	Yes <input type="radio"/> Y	No <input type="radio"/> N	Yes <input type="radio"/> Y	No <input type="radio"/> N	Yes <input type="radio"/> Y	No <input type="radio"/> N	Yes <input type="radio"/> Y	No <input type="radio"/> N	Yes <input type="radio"/> Y	No <input type="radio"/> N
External cooling	Yes <input type="radio"/> Y	No <input type="radio"/> N	Yes <input type="radio"/> Y	No <input type="radio"/> N	Yes <input type="radio"/> Y	No <input type="radio"/> N	Yes <input type="radio"/> Y	No <input type="radio"/> N	Yes <input type="radio"/> Y	No <input type="radio"/> N
Other cooling	Yes <input type="radio"/> Y	No <input type="radio"/> N	Yes <input type="radio"/> Y	No <input type="radio"/> N	Yes <input type="radio"/> Y	No <input type="radio"/> N	Yes <input type="radio"/> Y	No <input type="radio"/> N	Yes <input type="radio"/> Y	No <input type="radio"/> N
Intravenous opiate	Yes <input type="radio"/> Y	No <input type="radio"/> N	Yes <input type="radio"/> Y	No <input type="radio"/> N	Yes <input type="radio"/> Y	No <input type="radio"/> N	Yes <input type="radio"/> Y	No <input type="radio"/> N	Yes <input type="radio"/> Y	No <input type="radio"/> N

Completed by:
(print name)

Signature:

Date completed:

<input type="text"/>	<input type="text"/>	/	<input type="text"/>	<input type="text"/>	/	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
----------------------	----------------------	---	----------------------	----------------------	---	----------------------	----------------------	----------------------	----------------------

Appendix C

Steps taken to assess the association between heart rate and blood pressure using high-resolution data

1. *Temperature and site of measurement data for children admitted to PICU/NICU (excluding CICU) downloaded from the Philips IntelliSpace Critical Care and Anaesthesia electronic health record database using the following SQL query*

```
Select distinct en.lifeTimeNumber, en.encounterId, pass.chartTime,
intv.shortLabel, pass.verboseForm, att.shortLabel, pass.valueNumber
From dbo.PtAssessment as pass, dbo.D_Encounter as en, dbo.D_Intervention as
intv, dbo.D_Attribute as att
Where en.encounterId=pass.encounterId and att.attributeId=pass.attributeId and
intv.interventionId=pass.interventionId and
intv.shortLabel IN ('Temp. 1', 'Temp. 2', 'Temp. 3') and att.shortLabel in
('Temp', 'Site') AND
pass.chartTime BETWEEN '2016-01-01 00:00' AND '2016-12-31 23:59' AND
en.lifeTimeNumber in ('xxxxx',...);
```
2. *Temperature value and site matched as in Appendix A. Children who had core continuous temperature measurements (labelled oesophageal, rectal, core or bladder) identified and included.*
3. *High-resolution data for these children during the admission episodes extracted from the Etiometry T3 Data Sandpit (<http://gosh-etiomty03.pangosh.nhs.uk/study>) using individual hospital numbers*
4. *Temperature, heart rate, blood pressure data along with time stamp and hospital number manually collated into Microsoft Excel and stored as .csv files. Separate sequences assigned the first time in the sequence as the variable firsttime*
5. *Data exported into r*

```
#files assigned to variables as data frames (9 in total)
t1=read.csv("t3_picnic_2016_47048150_62963002.csv")
t2=read.csv("t3_picnic_2016_47564176_61239242.csv")
t3=read.csv("t3_picnic_2016_47564176_64305644.csv")
t4=read.csv("t3_picnic_2016_49862774_54694174.csv")
t5=read.csv("t3_picnic_2016_51360160_63680114.csv")
t6=read.csv("t3_picnic_2016_61286396_64265160.csv")
t7=read.csv("t3_picnic_2016_63034834_63096460.csv")
t8=read.csv("t3_picnic_2016_64305644_64579346.csv")
t9=read.csv("t3_picnic_2016_64602430_64778750.csv")
```

#individual vital signs assigned to single variables

```
temp=c(t1$temp,t2$temp,t3$temp,t4$temp,t5$temp,t6$temp,t7$Temp,8$temp,t9$temp)
```

```
hr=c(t1$hr,t2$hr,t3$hr,t4$hr,t5$hr,t6$hr,t7$HR..bpm.,t8$hr,t9$hr)
```

```
mbp=c(t1$mbp,t2$mbp,t3$mbp,t4$mbp,t5$mbp,t6$mbp,t7$ARTm,t8$mbp,t9$mbp)
```

```
sbp=c(t1$sbp,t2$sbp,t3$sbp,t4$sbp,t5$sbp,t6$sbp,t7$ARTs,t8$sbp,t9$sbp)
```

```
dbp=c(t1$dbp,t2$dbp,t3$dbp,t4$dbp,t5$dbp,t6$dbp,t7$ARTd,t8$dbp,t9$dbp)
```

```
alias=c(t1$alias,t2$alias,t3$alias,t4$id,t5$alias,t6$alias,t7$alias,t8$alias,t9$alias)
```

```
firsttime=c(t1$firsttime, t2$firsttime, t3$firsttime, t4$firsttime
```

```
t5$firsttime,t6$firsttime,t7$firsttime,t8$firsttime,t9$firsttime)
```

#variables censored according to a priori determined limits

```
temp32=temp[temp>=32]
```

```
hr32=hr[temp>=32]
```

```
alias32=alias[temp>=32]
```

```
firsttime32=firsttime[temp>=32]
```

```
mbp[mbp<16]=NA
```

```
mbp[mbp>233]=NA
```

```
mbp32=mbp[temp>=32]
```

```
sbp[sbp>250]=NA
```

```
sbp[sbp<30]=NA
```

```
sbp32=sbp[temp>=32]
```

```
dbp[dbp>200]=NA
```

```
dbp[dbp<10]=NA
```

```
dbp32=dbp[temp>=32]
```

6. *Multi-level linear regression analysis of heart rate and mean blood pressure to explore linear association with temperature*

```
fit.hr=lmer(hr32~temp32+(1|alias32)+(1|firsttime32))
```

```
fit.mbp=lmer(mbp32~temp32+(1|alias32)+(1|firsttime32))
```

```
fit.sbp=lmer(sbp32~temp32+(1|alias32)+(1|firsttime32))
```

```
fit.dbp=lmer(dbp32~temp32+(1|alias32)+(1|firsttime32))
```

7. *z-scores for heart rate and blood pressure similarly associated with temperature*

#age categorised by months of age according to categories in Fleming et al

```
agem=c(t1$agem,t2$agem,t3$agem,t4$agem,t5$agem,t6$agem,t7$agem,t8$agem,t9$agem)
```

```
agecat=c()
```

```
agecat[agem<3]=2
```

```
agecat[agem>=3 & agem<6]=3
```

```

agecat[agem>=6 & agem<9]=4
agecat[agem>=9 & agem<12]=5
agecat[agem>=12 & agem<18]=6
agecat[agem>=18 & agem<24]=7
agecat[agem>=24 & agem<36]=8
agecat[agem>=36 & agem<48]=9
agecat[agem>=48 & agem<72]=10
agecat[agem>=72 & agem<96]=11
agecat[agem>=96 & agem<144]=12
agecat[agem>=144 & agem<180]=13
agecat[agem>=180 & agem<216]=14
#l, m and s values from Fleming et al read into r from Microsoft Excel
flem=read.csv("Flemingcentiles.csv")
hrc=as.matrix(cbind(flem$X1c,flem$X10c,flem$X25c,flem$X50c,flem$X75c,flem$X90c,flem$X99c))
#lms matrix created using sitar package in r
lms.hr=LMSfit(x=c(1:14),y=hrc,sex=1,centiles=c(1,10,25,50,75,90,99))
#z-scores assigned sequentially in blocks of 500000
hrz=c()
for (i in
1:500000){hrz=c(hrz,zLMS(x=hr[i],L=lms.hr$LMS[agecat[i],3],M=lms.hr$LMS[agecat[i],4],S=lms.hr$LMS[agecat[i],5]))}
hrz1=hrz1
hrz1=hrz
for (i in
500000:1000000){hrz=c(hrz,zLMS(x=hr[i],L=lms.hr$LMS[agecat[i],3],M=lms.hr$LMS[agecat[i],4],S=lms.hr$LMS[agecat[i],5]))}
hrz1=hrz
hrz=c()
for (i in
1000001:1500000){hrz=c(hrz,zLMS(x=hr[i],L=lms.hr$LMS[agecat[i],3],M=lms.hr$LMS[agecat[i],4],S=lms.hr$LMS[agecat[i],5]))}
hrz2=hrz
hrz=c()
for (i in
1500001:2000000){hrz=c(hrz,zLMS(x=hr[i],L=lms.hr$LMS[agecat[i],3],M=lms.hr$LMS[agecat[i],4],S=lms.hr$LMS[agecat[i],5]))}

```

```

hrz2=c(hrz2,hrz)
hrz=c()
for (i in
2000001:2500000){hrz=c(hrz,zLMS(x=hr[i],L=ims.hr$LMS[agecat[i],3],M=ims.hr$LM
S[agecat[i],4],S=ims.hr$LMS[agecat[i],5]))}
hrz3=hrz
hrz=c()
for (i in
2500001:3000000){hrz=c(hrz,zLMS(x=hr[i],L=ims.hr$LMS[agecat[i],3],M=ims.hr$LM
S[agecat[i],4],S=ims.hr$LMS[agecat[i],5]))}
hrz3=c(hrz3,hrz)
hrz=c()
for (i in
3000001:3500000){hrz=c(hrz,zLMS(x=hr[i],L=ims.hr$LMS[agecat[i],3],M=ims.hr$LM
S[agecat[i],4],S=ims.hr$LMS[agecat[i],5]))}
hrz4=hrz
hrz=c()
for (i in
3500001:4000000){hrz=c(hrz,zLMS(x=hr[i],L=ims.hr$LMS[agecat[i],3],M=ims.hr$LM
S[agecat[i],4],S=ims.hr$LMS[agecat[i],5]))}
hrz4=c(hrz4,hrz)
hrz=c()
for (i in
4000001:5000000){hrz=c(hrz,zLMS(x=hr[i],L=ims.hr$LMS[agecat[i],3],M=ims.hr$LM
S[agecat[i],4],S=ims.hr$LMS[agecat[i],5]))}
hrz5=hrz
hrz=c()
for (i in
5000001:5500000){hrz=c(hrz,zLMS(x=hr[i],L=ims.hr$LMS[agecat[i],3],M=ims.hr$LM
S[agecat[i],4],S=ims.hr$LMS[agecat[i],5]))}
hrz6=hrz6
hrz6=hrz
hrz=c()
for (i in
5500001:6000000){hrz=c(hrz,zLMS(x=hr[i],L=ims.hr$LMS[agecat[i],3],M=ims.hr$LM
S[agecat[i],4],S=ims.hr$LMS[agecat[i],5]))}
hrz6=c(hrz6,hrz)

```



```

hrz=c()
for (i in
6000001:7000000){hrz=c(hrz,zLMS(x=hr[i],L=lms.hr$LMS[agecat[i],3],M=lms.hr$LM
S[agecat[i],4],S=lms.hr$LMS[agecat[i],5]))}
hr7=hrz
hrz7=hrz
t7=as.matrix(cbind(alias[6000001:7000000],hr[6000001:7000000],temp[6000001:700
0000],hrz7,agem[6000001:7000000],agecat[6000001:7000000],firsttime[6000001:70
00000]))
write.csv(t7,"t7.csv")
length(hr)
hrz=c()
for (i in
7000001:7535917){hrz=c(hrz,zLMS(x=hr[i],L=lms.hr$LMS[agecat[i],3],M=lms.hr$LM
S[agecat[i],4],S=lms.hr$LMS[agecat[i],5]))}
hrz8=hrz
#heart rate z-scores written into matrices with other variables
t1=as.matrix(cbind(alias[1:1000000],hr[1:1000000],temp[1:1000000],hrz1,agem[1:10
00000],agecat[1:1000000],firsttime[1:1000000]))
t2=as.matrix(cbind(alias[1000001:2000000],hr[1000001:2000000],temp[1000001:200
0000],hrz2,agem[1000001:2000000],agecat[1000001:2000000],firsttime[1000001:20
00000]))
t3=as.matrix(cbind(alias[2000001:3000000],hr[2000001:3000000],temp[2000001:300
0000],hrz3,agem[2000001:3000000],agecat[2000001:3000000],firsttime[2000001:30
00000]))
t4=as.matrix(cbind(alias[3000001:4000000],hr[3000001:4000000],temp[3000001:400
0000],hrz4,agem[3000001:4000000],agecat[3000001:4000000],firsttime[3000001:40
00000]))t5=as.matrix(cbind(alias[4000001:5000000],hr[4000001:5000000],temp[4000
001:5000000],hrz5,agem[4000001:5000000],agecat[4000001:5000000],firsttime[400
0001:5000000]))
write.csv(t5,"t5.csv")
t6=as.matrix(cbind(alias[5000001:6000000],hr[5000001:6000000],temp[5000001:600
0000],hrz6,agem[5000001:6000000],agecat[5000001:6000000],firsttime[5000001:60
00000]))
write.csv(t6,"t6.csv")

```

```

t7=as.matrix(cbind(alias[6000001:7000000],hr[6000001:7000000],temp[6000001:7000000],hrz7,agem[6000001:7000000],agecat[6000001:7000000],firsttime[6000001:7000000]))
write.csv(t7,"t7.csv")
t8=as.matrix(cbind(alias[7000001:7535917],hr[7000001:7535917],temp[7000001:7535917],hrz8,agem[7000001:7535917],agecat[7000001:7535917],firsttime[7000001:7535917]))
write.csv(t1,"t1.csv")
write.csv(t2,"t2.csv")
write.csv(t3,"t3.csv")
write.csv(t4,"t4.csv")
write.csv(t5,"t5.csv")
write.csv(t6,"t6.csv")
write.csv(t7,"t7.csv")
write.csv(t8,"t8.csv")

#multi-level regression analysis for zhr and temperature
hrz=c(hrz1,hrz2,hrz3,hrz4,hrz5,hrz6,hrz7,hrz8)
hrz32=hrz[temp>=32]
fit.hrz=lmer(hrz32~temp32+(1|alias32)+(1|firsttime32))

#z-scores for sbp according to sex from 4th report
sbpcent=read.csv("sysbpcent.csv")
f50h50=sbpcent$c50[sbpcent$sex==2]
f90h50=sbpcent$c90[sbpcent$sex==2]
f95h50=sbpcent$c95[sbpcent$sex==2]
m50h50=sbpcent$c50[sbpcent$sex==1]
m90h50=sbpcent$c90[sbpcent$sex==1]
m95h50=sbpcent$c95[sbpcent$sex==1]
fh50=as.matrix(cbind(f50h50,f90h50,f95h50))
mh50=as.matrix(cbind(m50h50,m90h50,m95h50))

#lms matrix created using centile data
lms.fh50=LMSfit(x=c(1:29),y=fh50,sex=2,centiles=c(50,90,95))
lms.mh50=LMSfit(x=c(1:29),y=mh50,sex=1,centiles=c(50,90,95))
msbp=sbp[sex==1]
fsbp=sbp[sex==2]
magecat=agecat[sex==1]
fagecat=agecat[sex==2]
mzsbp=c()

```

```

malias=alias[sex==1]
falias=alias[sex==2]
#z-scores for sbp calculated in blocks of 500000
for (i in
1:500000){mzsbp=c(mzsbp,zLMS(x=msbp[i],L=lms.mh50$LMS[magecat[i],3],M=lms.
mh50$LMS[magecat[i],4],S=lms.mh50$LMS[magecat[i],5]))}
mzsbp1=mzsbp
for (i in
500001:1000000){mzsbp=c(mzsbp,zLMS(x=msbp[i],L=lms.mh50$LMS[magecat[i],3],
M=lms.mh50$LMS[magecat[i],4],S=lms.mh50$LMS[magecat[i],5]))}
mzsbp1=mzsbp
mzsbp=c()
for (i in
1000001:1500000){mzsbp=c(mzsbp,zLMS(x=msbp[i],L=lms.mh50$LMS[magecat[i],3
],M=lms.mh50$LMS[magecat[i],4],S=lms.mh50$LMS[magecat[i],5]))}
mzsbp2=mzsbp
mzsbp=c()
for (i in
1500001:2000000){mzsbp=c(mzsbp,zLMS(x=msbp[i],L=lms.mh50$LMS[magecat[i],3
],M=lms.mh50$LMS[magecat[i],4],S=lms.mh50$LMS[magecat[i],5]))}
mzsbp2=c(mzsbp2,mzsbp)
mzsbp=c()
for (i in
2000001:2500000){mzsbp=c(mzsbp,zLMS(x=msbp[i],L=lms.mh50$LMS[magecat[i],3
],M=lms.mh50$LMS[magecat[i],4],S=lms.mh50$LMS[magecat[i],5]))}
mzsbp3=mzsbp
mzsbp=c()
for (i in
2500001:3000000){mzsbp=c(mzsbp,zLMS(x=msbp[i],L=lms.mh50$LMS[magecat[i],3
],M=lms.mh50$LMS[magecat[i],4],S=lms.mh50$LMS[magecat[i],5]))}
mzsbp3=c(mzsbp3,mzsbp)
mzsbp=c()
for (i in
3000001:3500000){mzsbp=c(mzsbp,zLMS(x=msbp[i],L=lms.mh50$LMS[magecat[i],3
],M=lms.mh50$LMS[magecat[i],4],S=lms.mh50$LMS[magecat[i],5]))}
mzsbp4=mzsbp
mzsbp=c()

```

```

for (i in
3500001:3718202){mzsbp=c(mzsbp,zLMS(x=msbp[i],L=lms.mh50$LMS[magecat[i],3
],M=lms.mh50$LMS[magecat[i],4],S=lms.mh50$LMS[magecat[i],5]))}
mzsbp4=c(mzsbp4,mzsbp)
mzsbp=c(mzsbp1,mzsbp2,mzsbp3,mzsbp4)

```

Steps repeated for females

```
#male and female data combined
```

```

zsbp=c(mzsbp,fzsbp)
temp=c(mtemp,ftemp)
alias=c(malias,falias)
firsttime=c(mfirsttime,ffirsttime)

```

```
#data for temperature <32 excluded
```

```

zsbp32=zsbp[temp>=32]
temp32=temp[temp>=32]
alias32=alias[temp>=32]
firsttime32=firsttime[temp>=32]

```

```
#multi-level regression analysis for zsbp and temperature
```

```
fit.zsbp=lmer(zsbp32~temp32+(1|alias32)+(1|firsttime32))
```

8. Steps repeated for diastolic and mean blood pressure

9. Non-linear association between heart rate and temperature explored by splitting data by 1°C intervals for temperature

```

temp3637=temp[temp>=36 & temp<37]
alias3637=alias[temp>=36 & temp<37]
hr3637=hr[temp>=36 & temp<37]
firsttime3637=firsttime[temp>=36 & temp<37]
agem3637=agem[temp>=36 & temp<37]
fit.hr3637=lmer(hr3637~temp3637+(1|alias3637)+(1|firsttime3637))
temp3738=temp[temp>=37 & temp<38]
alias3738=alias[temp>=37 & temp<38]
hr3738=hr[temp>=37 & temp<38]
firsttime3738=firsttime[temp>=37 & temp<38]
agem3738=agem[temp>=37 & temp<38]
fit.hr3738=lmer(hr3738~temp3738+(1|alias3738)+(1|firsttime3738))
temp3839=temp[temp>=38 & temp<39]

```

```

alias3839=alias[temp>=38 & temp<39]
hr3839=hr[temp>=38 & temp<39]
firsttime3839=firsttime[temp>=38 & temp<39]
agem3839=agem[temp>=38 & temp<39]
fit.hr3839=lmer(hr3839~temp3839+(1|alias3839)+(1|firsttime3839))
temp3940=temp[temp>=39 & temp<40]
alias3940=alias[temp>=39 & temp<40]
hr3940=hr[temp>=39 & temp<40]
firsttime3940=firsttime[temp>=39 & temp<40]
agem3940=agem[temp>=39 & temp<40]
fit.hr3940=lmer(hr3940~temp3940+(1|alias3940)+(1|firsttime3940))

```

Steps taken to assess the correlation between advanced haemodynamic variables and temperature using pulse contour analysis data

1. *Data downloaded as individual files from the LDCO rapid device*
2. *Temperature, paracetamol and confounder data added manually for each hour*
3. *Mean values for haemodynamic variables for 200 measurements around the hour calculated using following visual basic in Microsoft Excel*

```
Sub hour_point_avg()
```

```
Dim i, hrow, count, min, max As Double
```

```
Dim sum_ci, sum_svri, sum_hr, sum_map, sum_sv, sum_zHR, sum_sbp, sum_dbp
As Double
```

```
i = 2
```

```
hrow = 1
```

```
For i = 2 To 77161
```

```
If Cells(i, 23).Value > 1 Then hrow = i Else hrow = 1
```

```
  If hrow > 1 Then Cells(i, 24).Value = hrow
```

```
    Do While hrow > 1
```

```
      sum_ci = 0
```

```
      sum_svri = 0
```

```
      sum_hr = 0
```

```
      sum_map = 0
```

```
      sum_sv = 0
```

```
      sum_zHR = 0
```

```
sum_sbp = 0
```

```
sum_dbp = 0
```

```
min = hrrow - 100
```

```
max = hrrow + 100
```

```
count = min
```

```
For count = min To max
```

```
sum_ci = sum_ci + Cells(count, 4).Value
```

```
sum_svri = sum_svri + Cells(count, 8).Value
```

```
sum_hr = sum_hr + Cells(count, 15).Value
```

```
sum_map = sum_map + Cells(count, 11).Value
```

```
sum_sv = sum_sv + Cells(count, 14).Value
```

```
sum_zHR = sum_zHR + Cells(count, 53).Value
```

```
sum_sbp = sum_sbp + Cells(count, 10).Value
```

```
sum_dbp = sum_dbp + Cells(count, 12).Value
```

```
Next count
```

```
Cells(hrrow, 25).Value = sum_ci / 201
```

```
Cells(hrrow, 26).Value = sum_svri / 201
```

```
Cells(hrrow, 27).Value = sum_hr / 201
```

```
Cells(hrrow, 28).Value = sum_map / 201
```

```
Cells(hrrow, 29).Value = sum_sv / 201
```

```
Cells(hrrow, 30).Value = sum_zHR / 201
```

```
Cells(hrrow, 55).Value = sum_sbp / 201
```

```
Cells(hrrow, 56).Value = sum_dbp / 201
```

```
hrrow = 1
```

```
Loop
```

```
Next i
```

```
End Sub
```

4. Whole data set used for associations across the temperature range

```
#variables assigned from LiDCO data frame in r
```

```
stretch=LiDCO$stretch
```

```
temp=LiDCO$temp
```

```
ci=LiDCO$CI
```

```

svri=LiDCO$SVRI
hr=LiDCO$HR
map=LiDCO$MAP
svi=LiDCO$SVI
id=as.factor(LiDCO$id)
#correlation coefficients for 55 sequences of measurement calculated
cor.hr=c()
for(i in
1:55){cor.hr=c(cor.hr,cor(hr[stretch==i],temp[stretch==i],method="spearman"))}
cor.ci=c()
for(i in 1:55){cor.ci=c(cor.ci,cor(ci[stretch==i],temp[stretch==i],method="spearman"))}
cor.svi=c()
for(i in
1:55){cor.svi=c(cor.svi,cor(svi[stretch==i],temp[stretch==i],method="spearman"))}
cor.svri=c()
for(i in
1:55){cor.svri=c(cor.svri,cor(svri[stretch==i],temp[stretch==i],method="spearman"))}
cor.map=c()
for(i in
1:55){cor.map=c(cor.map,cor(map[stretch==i],temp[stretch==i],method="spearman"))
}
#length of each sequence calculated
length.stretch=c()
for(i in 1:55){length.stretch=c(length.stretch,length(hr[stretch==i]))}
#data written into .csv file
cor.LiDCO=as.matrix(cbind(unique(stretch),length.stretch,cor.hr,cor.svi,cor.ci,cor.svri
,cor.map))
write.csv(cor.LiDCO,"cor_LiDCO.csv")

```

5. *Analysis repeated with sequences where temperature rising to fever grade*

Steps taken to analyse the haemodynamic effects of paracetamol

1. *Univariable analysis using repeated measures analysis of variance*

```

#variables assigned to variables from data frame para
id=para$id

```

```

dose=as.factor(para$dose)
id=as.factor(id)
tp=as.factor(para$dosetime)
dose=para$para
mabp=para$mabp
hr=para$hr
svi=para$svi
ci=para$ci
svri=para$svri
sbp=para$sbp
dbp=para$dbp

```

#repeated measures analysis of variance according to time-point relative to paracetamol

```

fit.hr=aov(hr~tp+Error(id/dose))
fit.svi=aov(svi~tp+Error(id/dose))
fit.ci=aov(ci~tp+Error(id/dose))
fit.svri=aov(svri~tp+Error(id/dose))
fit.mabp=aov(mabp~tp+Error(id/dose))
fit.sbp=aov(sbp~tp+Error(id/dose))
fit.dbp=aov(dbp~tp+Error(id/dose))

```

2. *Multi-level linear regression models using a priori determined confounders*

#confounder variables assigned

```

id=as.factor(para$id)
tp=as.factor(para$dosetime)
dose=as.factor(para$para)
ino=as.factor(para$ino)
fluid=as.factor(para$fluid)
furos=as.factor(para$furos)
sed=as.factor(para$sed)
air=as.factor(para$map)
physio=as.factor(para$physio)
temp=para$temp
fever=as.factor(para$fever)

```

#multi-variable models created for each haemodynamic variable

```

fit.mabp=lmer(mabp~tp-1+ino+fluid+furos+sed+air+physio+route+(1|id)+(1|dose))
confint(fit.mabp)
fit.hr=lmer(hr~tp-1+ino+fluid+furos+sed+air+physio+route+(1|id)+(1|dose))

```



```

summary(fit.hr)
confint(fit.hr)
fit.svi=lmer(svi~tp-1+ino+fluid+furos+sed+air+physio+route+(1|id)+(1|dose))
confint(fit.svi)
fit.ci=lmer(ci~tp-1+ino+fluid+furos+sed+air+physio+route+(1|id)+(1|dose))
confint(fit.ci)
fit.svri=lmer(svri~tp-1+ino+fluid+furos+sed+air+physio+route+(1|id)+(1|dose))
confint(fit.svri)
fit.sbp=lmer(sbp~tp-1+ino+fluid+furos+sed+air+physio+route+(1|id)+(1|dose))
confint(fit.sbp)
fit.dbp=lmer(dbp~tp-1+ino+fluid+furos+sed+air+physio+route+(1|id)+(1|dose))
confint(fit.dbp)

```

#sub groups analysed for route of administration

```

fit.mabpiv=lmer(mabp[route=="IV"]~tp[route=="IV"]-
1+ino[route=="IV"]+fluid[route=="IV"]+furos[route=="IV"]+sed[route=="IV"]+air[route=
=="IV"]+physio[route=="IV"]+(1|id[route=="IV"])+(1|dose[route=="IV"]))
confint(fit.mabpiv)

```

3. *Effect of fever tested by comparing nested models with and without fever as an interaction term*

```

fit.mabpf=lmer(mabp~(tp*fever)+ino+fluid+furos+sed+air+physio+route+(1|id)+(1|dose))
confint(fit.mabpf)
lrtest(fit.mabp,fit.mabpf) #likelihood ratio test using the lrtest package

```

4. Exploring the relative effects of measured heart rate and stroke volume on change in blood pressure at time-point 2

#change in hr and svi between tp=2 and tp=0 calculated

```

deltahr=c()
for (i in 1:148){deltahr=c(deltahr,hr[tp==2 & para$para==i]-hr[tp==-1 &
para$para==i])}
deltasvi=c()
for (i in 1:148){deltasvi=c(deltasvi,svi[tp==2 & para$para==i]-svi[tp==-1 &
para$para==i])}
deltamabp=c()
for (i in 1:148){deltamabp=c(deltamabp,mabp[tp==2 & para$para==i]-mabp[tp==-1 &
para$para==i])}
#linear model fitted for change in mabp, change in hr and change in svi
fit.physiol=lm(deltamabp~deltahr+deltasvi)

```

summary(fir.physiol) #R2 value used to assess change in variance in mabp explained by change in variance of hr and svi

Appendix D

Steps taken to analyse association between ICU mortality and maximum temperature in the first 24 hours using retrospective temperature data from Great Ormond Street Hospital ICUs and FEAST dataset

1. *Data extracted as shown in Appendix A*
2. *Maximum temperature in the first 24 hours calculated in Microsoft Excel*
3. *Maximum temperatures categorised manually*
4. *Receiver operating characteristic curves with confidence intervals plotted in r using the pROC package*

```
roc.tmax=roc(status,tmaxna)
ci.auc(roc.tmax)
cise.tmax=ci.se(roc.tmax,specificities=seq(0,1,0.01),conf.level=0.95)
cihise.tmax=cise.tmax[,3]
cilose.tmax=cise.tmax[,1]
plot(roc(statusna,tmaxna))
polygon(c(seq(1,0,-
0.01),seq(0,1,0.01)),c(rev(cilose.tmax),cihise.tmax),col=rgb(147,147,147,max=255,al
pha=50),border=FALSE)
```

5. *Logistic regression analysis undertaken in r as follows*

```
#variables assigned from data frame comp
tmax=comp$tmax
status=comp$disstatus-1
pim=comp$PIMused
status=as.factor(status)
tmaxcat=as.factor(comp$tmaxcat)
#log regression model assigned to fit.tmax
fit.tmax=glm(status~tmaxcat-1+pim,family="binomial")
#coefficients calculated relative to reference category of 36.5-36.9°C
or.tmax=exp(fit.tmax$coefficients[1:10])
rr.tmax=or.tmax/or.tmax[3]
#confidence intervals calculated relative to reference category of 36.5-36.9°C
ci.tmax=confint(fit.tmax)
lci.tmax=exp(ci.tmax[1:10,1])
```

```

ruci.tmax=lci.tmax/lci.tmax[3]
uci.tmax=exp(ci.tmax[1:10,2])
ruci.tmax=uci.tmax/uci.tmax[3]
#relative risk of mortality according to temperature plotted
plot(rr.tmax~c(1:10),type="l",lwd=2,col="gray30",xlab="Maximum temperature in the
first 24 hours of admission (degrees C)",ylab="Adjusted odd ratios relative to 36.5-
36.9 degrees C",ylim=c(0,7),xaxt="n")
polygon(c(1:10,10:1),c(ruci.tmax,rev(ruci.tmax)),col=rgb(100,100,100,max=255,alpha
=50),border=FALSE)
axis(1,at=c(1:10),labels=c("<36","36.0-36.4","36.5-36.9","37.0-37.4","37.5-
37.9","38.0-38.4","38.5-38.9","39.0-39.4","39.5-39.9",>=40"))
abline(h=1,lty=2,col="gray50")

```

6. *Restricted cubic spline transformed maximum temperature used as a continuous variable in a logistic regression model in r. Hmisc and rms packages used.*

```

dd=datadist(tmax,pim)
dd$limits["Adjust to","tmax"]=36.5 #reference value set
options(datadist="dd")
quantile(tmax,probs=c(0.1,0.5,0.9),na.rm=TRUE) #10th, 50th and 90th centile values
calculated for knot positions
fit.tmax=lm(status~rcs(tmax,knots=c(37.0,37.7,38.7))+pim)
p=Predict(fit.tmax,tmax,ref.zero = TRUE)
#curve plotted
plot(p$tmax,exp(p$yhat),type="l",lwd=2,xlim=c(34,43),xlab="Maximum temperature
in the first 24 hours of admission (degrees C)",ylab="Adjusted odds ratio (95%
CI)",xaxt="n")
polygon(c(p$tmax,rev(p$tmax)),c(exp(p$lower),rev(exp(p$upper))),col=rgb(47,47,47,
max=255,alpha=50),border=FALSE)
abline(h=1,lty=2,lwd=2,col="gray50")
axis(1,at=c(34:41),labels=c(34:41))
points(c(37.0,37.7,38.7),c(0,0,0),pch=19)
#optimum temperature value determined manually by predicting risk over the range
of temperatures within which the nadir lies
p3738=Predict(fit.tmax,tmax=seq(37,38,0.01),ref.zero = TRUE)
p3738

```

7. *Analysis repeated for subgroups and FEAST dataset*

Analysis of the FEAST trial results according to presence or absence of fever at randomisation

1. Logistic regression model used for those with fever and those without fever at randomisation

```
#variables assigned according to presence of fever
```

```
fever=c()
```

```
fever[trand<38]=0
```

```
fever[trand>=38]=1
```

```
fever=as.factor(fever)
```

```
death=as.factor(feast$death)
```

```
mpet=feast$mPET_minustemp
```

```
#univariable models used for fluid arms and no fluid arm
```

```
fit.feast0=glm(death[fever==0]~fluid2[fever==0],family="binomial")
```

```
fit.feast1=glm(death[fever==1]~fluid2[fever==1],family="binomial")
```

```
summary(fit.feast0)
```

```
summary(fit.feast1)
```

```
exp(fit.feast0$coefficients)
```

```
exp(fit.feast1$coefficients)
```

```
exp(confint(fit.feast0))
```

```
exp(confint(fit.feast1))
```

```
#multivariable models used for fluid arms and no fluid arm
```

```
fit.feast0=glm(death[fever==0]~fluid2[fever==0]+mpet[fever==0],family="binomial")
```

```
fit.feast1=glm(death[fever==1]~fluid2[fever==1]+mpet[fever==1],family="binomial")
```

```
summary(fit.feast0)
```

```
summary(fit.feast1)
```

```
exp(fit.feast0$coefficients)
```

```
exp(fit.feast1$coefficients)
```

```
exp(confint(fit.feast0))
```

```
exp(confint(fit.feast1))
```

```
#forest plots created using forestplot package
```

```
tabletext=cbind(c("", "", "", "No fever", "Fever"),c("No fluid", "no. of deaths/no. of children (%)", "", "51/451 (11.3)", "25/590 (4.2)"),c("Fluid", "no. of deaths/no. of children (%)", "", "143/920 (15.5)", "93/1210 (7.7)"),c("", "OR (95% CI)", "", "1.44 (1.03-2.05)", "1.90 (1.23-3.04)"))
```

```

forestplot(tabletext,c(NA,NA,0,1.44,1.90),c(NA,NA,0,1.03,1.23),c(NA,NA,0,2.05,3.04)
,align="c",zero=1,lineheight=unit(28,"points"),xlab=c("Fluid better          No
fluid
better"),txt_gp=fpTxtGp(label=gpar(cex=0.8),xlab=gpar(cex=0.8),ticks=gpar(cex=0.8)
),lwd.zero=gpar(lwd=2,lty=2),graphwidth = unit(8,"cm"))

```

```

tabletext=cbind(c("", "", "", "No fever", "Fever"),c("No fluid", "no. of deaths/no. of children
(%)", "", "51/451 (11.3)", "25/590 (4.2)"),c("Fluid", "no. of deaths/no. of children
(%)", "", "143/920 (15.5)", "93/1210 (7.7)"),c("", "OR (95% CI)", "", "1.23 (0.85-
1.77)", "1.75 (1.09-2.88)"))

```

```

forestplot(tabletext,c(NA,NA,0,1.22,1.75),c(NA,NA,0,0.85,1.09),c(NA,NA,0,1.77,2.88)
,align="c",zero=1,lineheight=unit(28,"points"),xlab=c("Fluid better          No
fluid
better"),txt_gp=fpTxtGp(label=gpar(cex=0.8),xlab=gpar(cex=0.8),ticks=gpar(cex=0.8)
),lwd.zero=gpar(lwd=2,lty=2),graphwidth = unit(8,"cm"))

```

#effect of fever verified in a model using fever as an interaction term

```

fit.feast=glm(death~(fluid2*fever)+mpet,family="binomial")
exp(fit.feast$coefficients)
exp(confint(fit.feast))

```

continuous temp model of FEAST data using restricted cubic splines with 3 knots

```

library("rms", lib.loc=~R/win-library/3.6")
trand.fluid0=trand[fluid2==0]
trand.fluid1=trand[fluid2==1]
death.fluid0=death[fluid2==0]
death.fluid1=death[fluid2==1]
mpet.fluid0=mpet[fluid2==0]
mpet.fluid1=mpet[fluid2==1]
d0=datadist(trand.fluid0,mpet.fluid0)
d0$limits["Adjust to", "trand.fluid0"]=36.5
d1=datadist(trand.fluid1,mpet.fluid1)
d1$limits["Adjust to", "trand.fluid1"]=36.5
options(datadist="d0")
fit.fluid0=Irm(death.fluid0~rcs(trand.fluid0,knots=c(36.3,38.2,39.7))+mpet.fluid0)
p0=Predict(fit.fluid0,trand.fluid0,ref.zero=TRUE)
options(datadist="d1")

```

```

fit.fluid1=lm(death.fluid1~rcs(trand.fluid1,knots=c(36.4,38.1,39.6))+mpet.fluid1)
p1=Predict(fit.fluid1,trand.fluid1,ref.zero=TRUE)
plot(p0$trand.fluid0,exp(p0$yhat),type="l",lwd=2,xlab="Temperature at randomisation
(degrees C)", ylab="Adjusted odds ratio (95% CI)",
col=rgb(147,147,147,max=255),ylim=c(0,10),xlim=c(34,41))
polygon(c(p0$trand.fluid0,rev(p0$trand.fluid0)),c(exp(p0$lower),rev(exp(p0$upper))),
col=rgb(147,147,147,max=255,alpha=50),border=FALSE)
lines(p1$trand.fluid1,exp(p1$yhat),type="l",lwd=2,col="skyblue")
polygon(c(p1$trand.fluid1,rev(p1$trand.fluid1)),c(exp(p1$lower),rev(exp(p1$upper))),
col=rgb(135,206,235,max=255,alpha=50),border=FALSE)
points(c(36.3,38.2,39.7),c(0,0,0),pch=19,col=rgb(147,147,147,max=255))
points(c(36.4,38.1,39.6),c(-0.1,-0.1,-0.1),pch=19,col=rgb(135,206,235,max=255))
legend(40,9,legend=c("No fluids","Fluids"),lwd=2,col=c("gray50","skyblue"),bty="n")
abline(h=1,lty=2)

```