Variation in type 1 diabetes care of children and young people

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I, Dimitrios Charalampopoulos, 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

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Abstract

Background: For children with type 1 diabetes (T1D), achieving optimal glycaemic control is vital in reducing the risk of vascular complications. Despite national guidelines, many children fail to achieve target glycaemic goals. The thesis aimed to explore how HbA$_1c$, an important indicator of diabetes control, is distributed within and between clinics and also investigate the role of several aspects of diabetes services.

Methods: Variation in children’s HbA$_1c$ levels was analysed cross-sectionally and longitudinally via multilevel linear regression models using audit data from 41,860 children <19 years with T1D in England and Wales collected between 2005 and 2014. Workforce data were also collected across 175 UK services in 2014 to explore links between workforce features and glycaemic control. Finally, data from 64,666 children with T1D were analysed to compare variation in HbA$_1c$ between England and Wales and six other high-income countries in Europe and the USA.

Results: Differences between clinics accounted for 4-5% of the total variation in children’s glycaemic control, with variation within clinics being much more important. Children who attended clinics with less variable glycaemic levels had better glycaemic control [lower HbA$_1c$ by 9.8 mmol/mol (95% CI 8.2 to 11.5), per 10 mmol/mol decrease in clinic HbA$_1c$-SD]. Staffing levels varied considerably between the UK nations and only 43% of services provided 24-h access to advice from the team. However, staffing levels, clinic size, and regional networks made a limited contribution to explaining levels of HbA$_1c$. Population average HbA$_1c$ levels in England and Wales decreased by 6 mmol/mol between 2005 and 2014, however performance was poor when compared with Nordic countries.
Discussion: Nationwide improvements in glycaemic control might best be achieved not only by narrowing clinic differences but also by adopting a “whole system” approach that encourages changes in all clinics, no matter how well they perform.
**Impact statement**

For children with type 1 diabetes, achieving optimal glycaemic control is important in reducing the risk of vascular complications in the future. This thesis explored how HbA1c, an important indicator of diabetes control, is distributed within and between clinics in England and Wales. Findings showed that even if we are to eliminate all clinic differences, we will manage to confer improvements in only a small proportion (~4-5%) of the total variability in HbA1c. This is because most of the variability in children’s glycaemic control is located within clinics and is possibly attributed to individual factors on which clinics have limited control.

From the perspective of the diabetes team, the findings of this thesis suggest that in addition to achieving good overall results, clinics should also aim for greater consistency in their glycaemic performance. Achievement of higher homogeneity within a clinic will require focusing attention on the management of challenging groups of children, such as adolescents.

In terms of health policy, implementing interventions that primarily aim to reduce variations in paediatric diabetes care are unlikely to be sufficient in making nationwide improvements. Nationwide improvements in glycaemic control might best be achieved not only by narrowing clinic differences but also by focusing on the entire population of children with type 1 diabetes. This includes adopting a “whole system” approach that encourages changes in all clinics, even in some of the best performing clinics of the country.

The recent change in NICE guidelines towards tighter glycaemic targets might help towards this direction. However, this is unlikely to be sufficient in bringing about such
improvements. Patient-centred policies have been shown to be useful in stimulating whole system improvements. The recent introduction of patient reported experience measures in paediatric diabetes care in England and Wales is an important initiative which could help clinics across the country to identify aspects of care with the greatest potential to influence glycaemic outcomes.

England and Wales can also learn useful lessons from Sweden and other Nordic countries which have achieved homogeneously good glycaemic levels. These countries have long established a national program of continuous quality improvement in paediatric diabetes care which is based on transparent public reporting of centre performance, regular monitoring of variations, use of performance indicators as a clinical tool for professional development, and active participation of clinics in quality improvement “collaboratives”.

The quality of paediatric diabetes care in England and Wales is already monitored through a range of mechanisms. Diabetes care for children in England and Wales needs to move beyond a tick-box culture of inspecting compliance against minimum standards to a more meaningful assessment that focuses on bottom-up approaches which encourage local changes in all clinics, even those that perform well. The move to a continuous quality improvement model of care for diabetes requires a more systematic collection of individual-level data to measure performance, particularly on patient experience measures. However, it is important to ensure that such measures can be used effectively to inform clinicians’ professional development and clinical practice.
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<th>Full Form</th>
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<tbody>
<tr>
<td>ACDC</td>
<td>Association of Children’s Diabetes Clinicians</td>
</tr>
<tr>
<td>BPT</td>
<td>Best Practice Tariff</td>
</tr>
<tr>
<td>BSPED</td>
<td>British Society for Paediatric Endocrinology and Diabetes</td>
</tr>
<tr>
<td>CCT</td>
<td>Certificate of Completion of Training</td>
</tr>
<tr>
<td>CRD</td>
<td>Centre for Review and Dissemination</td>
</tr>
<tr>
<td>CSII</td>
<td>Continuous Subcutaneous Insulin Infusion</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular Disease</td>
</tr>
<tr>
<td>CYP</td>
<td>Children and Young People</td>
</tr>
<tr>
<td>DAFNE</td>
<td>Dose Adjustment for Normal Eating</td>
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<tr>
<td>DCCT</td>
<td>Diabetes Control and Complications Trial</td>
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<tr>
<td>DSN</td>
<td>Diabetes Specialist Nurse</td>
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<tr>
<td>DKA</td>
<td>Diabetic Ketoacidosis</td>
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<tr>
<td>EFSD</td>
<td>European Foundation for The Study of Diabetes</td>
</tr>
<tr>
<td>HQIP</td>
<td>Healthcare Quality Improvement Partnership</td>
</tr>
<tr>
<td>ICC</td>
<td>Intraclass Correlation Coefficient</td>
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<tr>
<td>IDHS</td>
<td>Identifiable Data Handling Solution</td>
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<tr>
<td>IFCC</td>
<td>International Federation of Clinical Chemistry</td>
</tr>
<tr>
<td>IMD</td>
<td>Indices of Multiple Deprivation</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>ISPAD</td>
<td>International Society for Paediatric and Adolescent Diabetes</td>
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<tr>
<td>LRT</td>
<td>Likelihood Ratio Test</td>
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<tr>
<td>MeSH</td>
<td>Medical Subject Heading</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>NCDR</td>
<td>Norwegian Childhood Diabetes Registry</td>
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<td>NPDA</td>
<td>National Paediatric Diabetes Audit</td>
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<tr>
<td>PDN</td>
<td>Paediatric Diabetes Networks</td>
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<tr>
<td>PDSN</td>
<td>Paediatric Diabetes Specialist Nurse</td>
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<tr>
<td>PDU</td>
<td>Paediatric Diabetes Unit</td>
</tr>
<tr>
<td>PREM</td>
<td>Patient Reported Experience Measures</td>
</tr>
<tr>
<td>PRISMA</td>
<td>Preferred Reporting Items of Systematic Reviews and Meta-Analysis</td>
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<tr>
<td>PROM</td>
<td>Patient Reported Outcome Measures</td>
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<tr>
<td>RCPCH</td>
<td>Royal College of Paediatrics and Child Health</td>
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<tr>
<td>RCT</td>
<td>Randomised Controlled Trials</td>
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<tr>
<td>SMD</td>
<td>Standardised Mean Difference</td>
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<tr>
<td>T1D</td>
<td>Type 1 Diabetes</td>
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<tr>
<td>UCL</td>
<td>University College London</td>
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<tr>
<td>VPC</td>
<td>Variance Partitioning Coefficient</td>
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<td>WTE</td>
<td>Whole Time Equivalent</td>
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Chapter 1  Introduction

1.1  Type 1 diabetes: definition, pathophysiology, and diagnosis

Type 1 Diabetes (T1D) is a chronic disease characterised by lack of insulin production which leads to a lifelong dependency on insulin (1). T1D is the most common form of diabetes during childhood and accounts for 5-10% of all diagnosed cases of diabetes. T1D results from a combination of genetic predisposition and autoimmune processes involving the destruction of the insulin-producing pancreatic beta-cells (2).

Insulin is an important anabolic hormone as it promotes cellular utilisation and storage of glucose, utilisation of amino acids and fat synthesis (3). When insulin is absent, glucose cannot enter cells and remains in the blood causing hyperglycaemia. Low levels of glucose uptake and utilisation forces cells to go into fasted-state metabolism that entails breaking down their fat stores (3). Plasma fatty acids are further metabolised in the liver in a process called β-oxidation which leads to the formation of ketone bodies that can be used in some tissues for energy (4). However, ketone bodies are acids and can cause metabolic acidosis (diabetic ketoacidosis-DKA).

The clinical onset of T1D may be preceded by an asymptomatic period of a few months to years, during which pancreatic beta-cells are undergoing gradual destruction. Presenting symptoms of T1D usually include polyuria (excessive urination), polydipsia (excessive thirst), polyphagia (excessive hunger), dehydration, and weight loss (3). In the presence of symptoms, the diagnosis is confirmed by measurement of elevated blood glucose levels and may require continued observation with fasting plasma glucose and/or oral glucose tolerance test (5).
Prolonged levels of high glucose in the blood cause generalised vascular damage affecting several tissues and organs including the heart, eyes, kidneys, and nerves. Diabetes is one of the leading causes of cardiovascular disease (CVD), blindness, renal failure and lower-limb amputation (6). Complications of T1D can be divided into two broad categories: acute and chronic complications. Acute complications include hypoglycaemia, DKA, and infections. Chronic complications can be categorised into micro- and macrovascular. Microvascular complications include nephropathy, neuropathy and retinopathy, whereas macrovascular complications include coronary heart disease, peripheral arterial disease, diabetic foot and encephalopathy (4).

1.2 Epidemiology of type 1 diabetes

In most countries, T1D accounts for more than 90% of diabetes in children (7). About 50-60% of individuals with T1D are diagnosed before the age of 15 (7). The incidence of T1D in paediatric populations shows considerable between-country variation with the number of newly diagnosed cases per 100,000 children per year varying from less than one in Peru to more than 35 in Finland (8). Over the last few years, there has been a well-recognised increase in the incidence of T1D with an average yearly rate of 3.2% in Europe and 2.8% worldwide (9). There is some indication of geographical differences in trends with some Eastern and Central European countries demonstrating a steeper increase. The reasons for this increase are unclear. However, it is hypothesised that this may be due to changes in environmental factors or viral infections.

The number of new cases in Europe is predicted to rise from 15,000 in 2005 to 24,400 in 2020 with a doubling in the number of pre-school children (10). With a prevalence
of 40,300 children under 20 years with T1D in 2017, the United Kingdom (UK) has
the second largest paediatric T1D population in Europe and the seventh largest in the
world (6). The UK also has the sixth highest incidence rate of T1D in the world, with
about 4,000 children under the age of 20 being diagnosed each year (6).

As compared to the general population, risk of death from all causes in patients with
T1D is twice as high among patients with Glycated Haemoglobin HbA1c (i.e. a useful
marker of longer-term glycaemic control) of equal or less than 52 mmol/mol (6.9%)
and 8 times as high among patients with very poor glycaemic control (HbA1c ≥ 83
mmol/mol (9.7%)) (11). The excess mortality among patients with T1D is mainly due
to development of long-term macro- and microvascular complications and, to a lesser
extent, due to acute complications including DKA and hypoglycaemia (12).

1.3 Management of type 1 diabetes

Management of T1D in children and adolescents is complex and requires a
comprehensive package of care where children and their carers are educated to make
informed decisions about the proper use of insulin treatment, diet, physical activity
and lifestyle choices, effective monitoring of blood glucose, blood pressure, lipids, and
regular screening for complications (2). Education of children and carers both at
diagnosis and during follow-up is an integral part of diabetes care. Children can
develop diabetes at different developmental stages and may come from diverse ethnic,
socioeconomic, and cultural backgrounds. Therefore, management of diabetes needs
to be individually tailored to meet children’s and families’ conditions and will need to
be adjusted as the child grows.
Insulin treatment is the primary medication for children with T1D. Insulin is given by injection usually via an insulin pen. Although twice-daily injections have long been the traditional method for administering insulin, a multiple daily injection scheme provides a better match to the physiological insulin profile (2). An alternative to injections is the use of insulin pump therapy, also called continuous subcutaneous insulin infusion (CSII). In this type of insulin delivery, a small pump about the size of a pack of playing cards delivers a continuous infusion of insulin via a subcutaneous catheter (2).

Children with T1D require access to regular, systematic, and organised care provided by a group of appropriately trained healthcare professionals (5). Children and young people with T1D in the UK are typically managed by multidisciplinary teams based on hospital-based Paediatric Diabetes Units (PDU). Members of the multidisciplinary team usually include a consultant paediatrician, a diabetes specialist nurse, a dietician or nutritionist, and a mental health professional (most frequently clinical psychologist) (5). The team may also enlist other professionals, including a diabetes educator, a podiatrist, and other clinicians.

1.4 Conceptualisation of paediatric diabetes care

Management of T1D requires complex contributions from various elements of a healthcare system. A comprehensive and structured way to conceptualise diabetes care is to distinguish between three successive elements that constitute the “input-processes-outcomes” framework (13) (Figure 1). In the context of T1D, this framework provides a useful and meaningful way to conceptualise the flow of care from available resources to health outcomes (2).
Inputs are the resources needed for the provision of diabetes care to children. These include staffing levels, composition, training and experience of diabetes team, funding, and availability of psychologist or 24-hour support. Inputs are also closely linked to structural aspects of health systems. In this regard, factors such as clinic volume, and organisation of clinics into regional networks can play a key role in the way available resources are organised to provide diabetes care.

The second element is processes of care. Care processes refer to how available resources are utilised and include all activities that are essential in the delivery of diabetes care. Such processes include frequency of clinic visits, metabolic monitoring and screening for cardiovascular complications, delivery and content of patient psycho-educational programs, implementation of guidelines, and patient-staff interaction. Traditionally, processes of care have been one of the most important components of quality management in paediatric diabetes as they are easy to measure, they are sensitive to quality of care, and they can provide clear pathways for action (2). For example, findings from the England and Wales NPDA reports have consistently shown a 13-fold variation (range from 7.7% to 100%) in the proportion of children and young people who did not receive all recommended care processes across diabetes units (14). However, the primary focus on processes of care assumes that improvements in the delivery of care will result in better health outcomes. This might not necessarily be the case.

Finally, outcomes are the end results of care that can be measured in terms of changes in patient’s physical health status or quality of life. Outcomes are often more meaningful to stakeholders and have a strong focus on the patient (15). In T1D, these include quality of life, levels of glycated haemoglobin (HbA1c), complications, and
other outcomes. Among those outcomes, HbA$_1c$ is a particularly important intermediate outcome for children with T1D, and it is further discussed below.
Figure 1. Diagram showing the “input-processes-outcomes” framework for paediatric diabetes care.
1.5 Glycated Haemoglobin HbA\textsubscript{1c} as a marker of longer-term glycaemic control

When haemoglobin and other proteins are exposed to glucose, the glucose becomes attached to the protein in a concentration-dependent fashion (4). Therefore, measurement of plasma levels of HbA\textsubscript{1c} reflects the average glucose concentration over the preceding 2-3 months thereby providing a useful marker of an individual’s longer-term glycaemic control (3). Since 2011 and in line with other European countries, the way HbA\textsubscript{1c} values are reported in the UK has switched from a percentage [known as the Diabetes Control and Complications Trial (DCCT) units] to a measurement in mmol/mol [known as the International Federation of Clinical Chemistry (IFCC) units]. In the current thesis HbA\textsubscript{1c} measurements will be reported, where possible, in IFCC units (mmol/mol) together with DCCT units (%) in brackets.

Glycaemic control, as assessed by plasma levels of HbA\textsubscript{1c}, is one of the most important modifiable risk factors linked to the future development of chronic vascular complications. In fact, two landmark studies have provided convincing evidence for a clear link between glycaemic control and the development of complications in individuals with T1D. The Diabetes Control and Complications Trial (DCCT) studied about 1,400 adolescents and young adults diagnosed with T1D for 1-5 years. Participants were randomised to receive intensive (3 or more insulin injections per day or use of pumps) or conventional (one or two insulin injections per day) treatment and were followed for an average of 6.5 years (16). Findings showed that reduction in HbA\textsubscript{1c} by 1% as part of intensive treatment conferred a 43% reduction in risk of retinopathy and macroalbuminuria, and 25-30% reduction in risk of microalbuminuria and neuropathy, thus highlighting the importance of optimising metabolic control for
the development of early microvascular complications (16). The Epidemiology of Diabetes Interventions (EDIC) was an observational study that followed the DCCT cohort for a period needed to determine the role of intensive insulin treatment on longer-term macrovascular complications. An 18-year follow-up of the DCCT/EPIC cohort showed that the former intensive arm had a 42-58% reduction in the risk of cardiovascular complications (16).

Based on the above evidence, the National Institute for Health and Care Excellence (NICE) guidelines highlight the importance of children achieving good glycaemic control. Although a target level of HbA1c less than 58 mmol/mol (7.5%) was recommended up until 2015 (17), data from the National Paediatric Diabetes Audit (NPDA) have shown that about five in six Children and Young People (CYP) in England and Wales fail to meet the NICE glycaemic target, thus, putting themselves at an increased risk of complications (18). New NICE guidelines were introduced in August 2015 setting stricter targets of below 48 mmol/mol (6.5%) for children with T1D (19). Commitment to a strict glycaemic control also imposes significant psychological and emotional burdens on children and their families. Children with diabetes have an increased risk of developing a psychiatric disorder during the first decade after diagnosis, with depression, anxiety, behavioural and conduct disorders being the most common (20, 21). Presence of psychiatric disorders is also adversely related to metabolic control, presumably by impacting on diabetes self-care and well-being (22-24).
1.6 Variation in glycaemic control: conceptualisation and controversies

In 2012, publication of the NHS Diabetes Atlas of Variation showed that both treatment targets and diabetes outcomes vary significantly across regions in England. In fact, data from children aged 0-15 years revealed a 7-fold variation in recurrent DKA admissions and a 2.4-fold variation in the percentage of children with HbA1c < 86 mmol/mol (10%) between Primary Care Trusts (25). The fact that variation in glycaemic control and other diabetes outcomes exists is unsurprising. The critical question, however, is what the sources of this variation are, or to put it differently, what proportion of the variation is potentially unavoidable or justifiable and what is not.

There are different ways to conceptualise variation in children’s glycaemic control. A comprehensive way to conceptualise variation is to map all possible factors that can exert an influence on children’s glycaemic outcomes, from inaccuracies of data collection and random variation to factors related to demand and supply of diabetes care (26) (see Figure 2). The list of potential factors cannot be exhaustive, and this approach illustrates all the complexities and interactions between the contributing factors.

Another useful and more straightforward way to think about variation in diabetes care is to distinguish between factors that are within the control of health services and those that are outside such control. For example, it is recognised that some of the variations in healthcare might reflect patient preferences or factors over which health services have little or no control. Wennberg coined the term “unwarranted variation” to describe the variation in healthcare services that cannot be explained by differences in
patient preferences or patient illness (27). In other words, unwarranted variation reflects the portion of the variability in outcomes which is related to the way that healthcare is structured and delivered or to patients not gaining access to the appropriate level of intervention according to their needs.

Figure 2. Mapping sources of variation in glycaemic control of children with type 1 diabetes; figure adapted from Appleby et al. (2011).
Analysis of variation in healthcare has long been a source of controversy. A typical response of clinicians and health organisations when variations in health services are discussed is that “our patients are different”. A standard principle of adjustment is to only control for outcome determinants that are outside the control of the provider (28). Such adjustment attempts to remove the effect of differences between providers in such factors as age, gender, and case-mix of the population. For example, age is a classic confounder in epidemiology and a well-known risk factor for glycaemic control. In fact, adolescents with T1D are more likely to have poorer glycaemic control as compared to younger children. In this regard, it would be unfair not to consider the age of children when comparing the glycaemic performance of clinics with different age profiles. Other common factors that are usually included in case-mix adjustment in diabetes research include gender, comorbidities (e.g. coeliac or thyroid disease) and factors related to disease stage or severity (e.g. diabetes duration).

However, the question of which factors should be included in the case-mix adjustment does not always have a simple answer. For example, there is much debate about whether factors like deprivation and ethnicity should be adjusted for when provider performance is compared. On the one hand, small-area deprivation captures a range of factors exogenous to the clinic environment, such as education, financial status, housing, environmental pollution and can also act as a proxy for lifestyle and family environment, all of which influence patient’s glycaemic control. On the other hand, however, it could be argued that it is up to providers to meet children’s needs regardless of their ethnic background or socioeconomic status.
1.7 The National Paediatric Diabetes Audit (NPDA)

Most of the analyses of the current PhD were conducted on national data from the NPDA. The NPDA is an audit of the care processes and outcomes achieved by all children and young people attending PDUs where care is provided in England and Wales (http://www.rcpch.ac.uk/national-paediatric-diabetes-audit-npda). The NPDA is delivered by the Royal College of Paediatrics and Child Health (RCPCH), commissioned by the Healthcare Quality Improvement Partnership (HQIP) and funded by NHS England and the Welsh Government. Participation in the NPDA is a mandatory requirement to receive the diabetes tariff in England. Each PDU submits data annually to the NPDA.

1.8 PhD structure

The current thesis will make use of the wealth of national data being collected in paediatric diabetes units across England and Wales with the aim of exploring the impact of clinic context and several aspects of diabetes services on children’s glycaemic control. Since glycaemic control is one of the most important modifiable risk factors for children with T1D, the central theme of this PhD thesis is to explore variation in glycaemic control.

More specifically, the thesis is structured into nine chapters. The first chapter provides a short introduction to T1D and explores the concept of variation in the context of paediatric diabetes care. The following two chapters (chapters 2 and 3) review the literature and synthesise existing evidence from observational and experimental studies on the role of clinic context in glycaemic control and other important diabetes outcomes for children and young people with T1D. More specifically, the first
systematic review (chapter 2) explores how previous observational studies have quantified variation in glycaemic control and other diabetes outcomes and also provides a narrative synthesis of available evidence for the association of diabetes outcomes with different aspects of care related to inputs, structure, and care delivery. The second systematic review and meta-analysis (chapter 3) focuses on children’s psycho-educational programs, one of the most important processes of diabetes care. Following a discussion on the effectiveness of such programs in the international context, the review synthesises evidence from UK-based randomised controlled trials on the effectiveness of psycho-educational programs in improving glycaemic control and psychosocial functioning in children and young people with T1D. The review also attempts to explain why interventions do not seem to “work” in the UK by drawing useful comparisons with successful implementation of similar US interventions.

Chapters 4-6 analyse cross-sectional national audit data in England and Wales to examine the role that clinic context plays in understanding differences in children’s glycaemic control. Chapter 4 explores the magnitude of variation between diabetes clinics and highlights the importance of considering clinic variation as a share of the total variability in HbA1c. The question to be asked here is what the scope of improving children’s glycaemic control is by narrowing differences between clinics. Chapters 5 and 6 set out to examine whether specific aspects of diabetes care can help us explain differences between clinics and their association with children’s glycaemic levels. More specifically, chapter 5 discusses whether the influence of clinic context can be explained by differences in insulin regimen and clinic factors such as the organisation of clinics into regional networks, clinic volume, and within-clinic variability. Chapter 6 concentrates on the role of paediatric diabetes workforce, one of the most important inputs to diabetes care. As part of the current thesis, workforce data were collected
across paediatric diabetes services in the UK. Differences in staffing levels between the four UK nations and across England regional networks are presented, and associations between workforce features and children’s glycaemic control in England and Wales are explored by linkage to national audit data.

Chapters 7 and 8 seek to give a broader perspective (in terms of place and time) of clinic variation in children’s glycaemic control for England and Wales. Chapter 7 compares England and Wales with six other high-income countries in Western Europe and the USA. Findings of this large international study are explained in the context of existing literature and knowledge of health policy in the various countries. Chapter 8 uses national audit data in England and Wales over the last decade to explore changes in the mean glycaemic control and clinic variation over time.

Finally, chapter 9 brings all findings of the thesis together, suggests new avenues for research and makes clear recommendations about how findings of the thesis can be used to influence health policy decisions in order to optimise quality improvement initiatives in England and Wales.

1.9 Patient involvement

As part of the current thesis, children and young people with T1D have been involved at the dissemination stage through the close collaboration of the Policy Research Unit in the Health of Children, Young People and Families (CPRU) with the National Children’s Bureau. This involvement included a workshop which was attended by young people with T1D and parents. The workshop included several discussion sessions and interactive activities designed to encourage the group to share their views on what they found interesting, surprising or confusing about the research as well as
to provide feedback on the best way to communicate the findings, reflect on the practical implications of the findings and development of future projects.

1.10 Data protection, ethics, and permissions

Guidance on the use of patient data for the current thesis was sought from appropriate authorities (UCL Research Ethics Committee). Ethics approval was not required since this was a secondary analysis of the existing audit (see Appendix A). The NPDA has section 251 approval to collect and hold patient information for the audit without written consent (Reference No: ECC 2-03 (c)/2012). Patients and their parents are informed of the submission of their data to the NPDA by the local PDU. The UCL Great Ormond Street Institute of Child Health has an established infrastructure to handle sensitive and confidential data. Access to the ICH building is card-controlled, and CCTV is in use. All data were accessed and retrieved using the Identifiable Data Handling Solution (IDHS) secure technical environment. No personal identifiers were released, and all subsequent analyses were conducted on pseudo-anonymised datasets. Permission to access and analyse national audit data has been granted by HQIP as the data controllers. The current study is registered with the Joint Research and Development Office, GOS Institute of Child Health, UCL (Project No: 14PP09) and the UCL Data Protection Office (registration No Z6364106/2014/03/125). Permission has been granted by John Wiley & Sons and by the American Diabetes Association to reproduce Figures and Tables from chapters 4-7.
Chapter 2  **Between centre variation in diabetes outcomes and associations with aspects of service delivery: a systematic review of observational studies on children and young people with type 1 Diabetes**

2.1  **Introduction**

T1D is one of the most common chronic diseases in childhood and adolescence, with an incidence of 28.2 new cases per 100,000 children under the age of 14 in the United Kingdom (UK) every year (29). The increasing burden of paediatric diabetes has a substantial impact on health care services thus demonstrating the need for appropriate health care planning and delivery.

In the UK, children and young people (CYP) with T1D are usually managed by multidisciplinary teams in hospital-based diabetes clinics. Delivery of efficient and effective diabetes services underpins the achievement of optimal glucose control with the aim of reducing the risk of complications in later life. The gold standard for assessing average glucose control over the preceding 2-3 months is Glycated Haemoglobin A\textsubscript{1c} (HbA\textsubscript{1c}), and regular testing is recommended to guide management advice. NICE has recently recommended a target for HbA\textsubscript{1c} of 6.5% (48 mmol/mol) or lower (19). In order to achieve improvements in metabolic control, current clinical guidelines recommend that children and adolescents with T1D be managed by a multidisciplinary team, including specialist support from paediatricians, nurses, dieticians and psychologists (19). Although it is widely accepted that lower glycaemic
targets confer a significant reduction in risk of diabetes-related complications (16), only 6.4% of children cared for in clinical services in England and Wales meet this target (30).

There is extensive literature exploring individual risk factors for glycaemic control in children with T1D. However, the role of the clinic environment in shaping glycaemic outcomes has not been robustly investigated. Variation in health outcomes between different healthcare providers can be attributed to both the profile of patients being served by particular clinics (case-mix variation) as well as the nature of the clinical environment in which care is provided (contextual variation) (31). In order to make informed decisions about differences between healthcare providers, case-mix variation should be adequately adjusted for (32). Finally, although optimal management of paediatric diabetes requires considerable resources, there is no clear evidence as to which elements of diabetes delivery have the potential to drive improvements in diabetes outcomes.

2.1.1 Objectives of the systematic review

The current systematic review has two objectives. First, to describe the magnitude and evaluate the evidence for variation in glycaemic control and other diabetes outcomes between clinics as provided by multi-centre studies in CYP with T1D. Unexplained differences between clinics indicate that clinic context might exert an influence on diabetes outcomes. An additional objective is to provide a narrative synthesis of available evidence from non-interventional studies for the association between specific aspects related to the delivery of paediatric diabetes care and diabetes outcomes including glycaemic control and hospital admissions.
2.2 Methods

2.2.1 Search strategy

A literature search was conducted to identify studies reporting on variation between clinics or aspects of service delivery in paediatric diabetes populations. Medline, EMBASE, and CINAHL were systematically searched for relevant citations up to June 2015. A combination of keywords and MeSH (Medical Subject Headings) terms were used to create four subsets of citations: one relating the exposure (between-clinic variation and service delivery), a second indexing the outcomes of interest (glycaemic control and diabetic ketoacidosis (DKA) or hypoglycaemic admissions) a third relating to target population (type 1 diabetes), and a fourth related to study design (observational studies or clinical audits). Results were then limited to humans, children and young adults up to the age of 24 years, English language and year of publication (last 20 years). Restrictions in publication year were imposed to capture current evidence which allows comparability between healthcare systems. The search strategy used in Medline is presented in Table 1. A similar search strategy was followed in the other databases.

2.2.2 Eligibility criteria

Studies were included if they were observational studies (cross-sectional, longitudinal, case-control) or clinical audits; conducted in children and young people up to the age of 24 with T1D; explored between-centre variation formally testing differences between clinics in diabetes outcomes or/and investigate the association between a clearly defined indicator of service delivery (including factors related to input, structure, and process of diabetes care) and a diabetes outcome by providing a measure
of association. The outcomes of interest were glycaemic control (measured as levels of HbA$_1c$ or % of children meeting a specific HbA$_1c$ target) or/and DKA or hypoglycaemic admissions. Studies examining DKA admissions only at diagnosis were excluded since this outcome is unlikely to be affected by factors related to diabetes care. Letters, editorials, reviews, qualitative studies, notes and studies conducted on animals were excluded. Also studies on transition to adult care were excluded if they included participants outside the eligible age range specified in the current review. Experimental studies such as randomised controlled trials investigating the effectiveness of psychological and educational interventions on diabetes outcomes are the focus of the next chapter and were excluded from the current review.
### Table 1. Search Strategy (Medline via Ovid)

<table>
<thead>
<tr>
<th>Search terms</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Health Services/</td>
<td>19,434</td>
</tr>
<tr>
<td>2. Child Health Services/</td>
<td>17,859</td>
</tr>
<tr>
<td>3. Adolescent Health Services/</td>
<td>4,572</td>
</tr>
<tr>
<td>4. Health Resources/</td>
<td>9,311</td>
</tr>
<tr>
<td>5. Delivery of Health Care /</td>
<td>68,028</td>
</tr>
<tr>
<td>6. (clinic adj2 (visit* or attendance))</td>
<td>8,102</td>
</tr>
<tr>
<td>7. Quality of Health Care /</td>
<td>59,407</td>
</tr>
<tr>
<td>8. multidisciplinary or MDT or workforce or caseload or staff* or contact or telephone or text</td>
<td>573,498</td>
</tr>
<tr>
<td>9. (care or healthcare or &quot;health care&quot; or service* or centre* or clinic*) adj3 (patient* or family* or quality or organisation or delivery or model or diabet* or access or specialist or resource*)</td>
<td>762,203</td>
</tr>
<tr>
<td>10. (variation or difference*) adj3 (service* or centre* or clinic* or hospital*)</td>
<td>32,922</td>
</tr>
<tr>
<td>11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10</td>
<td>1,314,329</td>
</tr>
<tr>
<td>12. (metabolic or diabet* or glucose* or glycemic or glycaemic) adj5 (management or control or outcome*)</td>
<td>131,105</td>
</tr>
<tr>
<td>13. Diabetic Ketoacidosis/</td>
<td>5,238</td>
</tr>
<tr>
<td>14. &quot;diabetic ketoacidosis&quot; or dka or hypoglyc*</td>
<td>89,984</td>
</tr>
<tr>
<td>15. HbA1c or A1c or &quot;HbA(1c)&quot; or &quot;glycosylated haemoglobin&quot;</td>
<td>30,699</td>
</tr>
<tr>
<td>16. Haemoglobin A, Glycosylated/</td>
<td>24,410</td>
</tr>
<tr>
<td>17. 12 or 13 or 14 or 15 or 16</td>
<td>210,982</td>
</tr>
<tr>
<td>18. ((&quot;type 1&quot; or &quot;type I&quot; or paediatric or paediatric or child* or young or youth* or juvenil* or (insulin adj depend*) or insulin-depend* or teen* or adolescen*)) adj4 (diabet* or DM)</td>
<td>94,482</td>
</tr>
<tr>
<td>19. exp Diabetes Mellitus, Type 1/ or (T1DM or DM1 or T1D or IDDM)</td>
<td>67,249</td>
</tr>
<tr>
<td>20. 18 or 19</td>
<td>96,245</td>
</tr>
<tr>
<td>21. 11 and 17 and 20</td>
<td>4,875</td>
</tr>
<tr>
<td>22. Epidemiologic studies/ or exp case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or Cross sectional.tw. or Cross-sectional studies/ or exp Medical Audit/ or exp Clinical Audit/ or exp Nursing Audit/</td>
<td>2,075,619</td>
</tr>
<tr>
<td>23. 21 and 22</td>
<td>1,562</td>
</tr>
<tr>
<td>24. limit 23 to (humans and (&quot;all child (0 to 18 years)&quot; or &quot;young adult (19 to 24 years)&quot;))</td>
<td>790</td>
</tr>
<tr>
<td>25. limit 24 to (english and last 20 years)</td>
<td>665</td>
</tr>
</tbody>
</table>
2.2.3 Study selection and data extraction

References obtained by literature searches were entered into Endnote. After removal of duplicates, titles and abstracts of unique references were screened against the eligibility criteria described above and for potentially eligible articles full text was obtained. Bibliographies of selected studies were hand-searched for additional eligible studies not found in the initial literature search. A predetermined set of information was extracted from each eligible study. Extracted information included characteristics of the studies (such as first author, date of publication, country, and study design), participant characteristics (number of study participants, selection criteria), types of indicators for service delivery used, reported diabetes outcomes, statistical analysis, and main findings.

2.3 Results

Overall, 1,246 unique citations were identified from literature searches. After title and abstract screening of those citations against the eligibility criteria, 1,070 citations were excluded, leaving 176 potentially eligible articles for full-text screening. Finally, 20 studies were found eligible for inclusion in the current systematic review (see Figure 3).

2.3.1 Description of studies

Of the 20 studies, 6 were conducted in the UK (33-38), three in the USA (39-41), two in Germany/Austria (42, 43) and from one in France (44), Belgium (45), Australia (46), Sweden (47), and Denmark (48). Four articles (49-52) reported on results from the same multicentre international study across 19 countries. The majority of studies
had a cross-sectional design, except for five longitudinal studies (37, 39, 42, 45, 48) and three clinical audits (33-35).

Figure 3. Flow diagram for selection of studies
2.3.2 Variation in diabetes outcomes between clinics: evidence from multi-centre observational studies

Eight multi-centre studies (37, 38, 43, 47-51) which were published between 2001 and 2013 reported on the magnitude of between-clinic variation in diabetes outcomes. Only three studies used nationally representative data covering a proportion of 80% or higher of the population of children with T1D in their respective countries (38, 43, 48). Of the eight studies, three (49-51) reported results from the same international study, however referring to different time points and different populations of children with T1D. Table 2 presents the characteristics and detailed results of the studies.

All but one study (43) used traditional statistical methods to analyse clinic differences operating only at the level of the individual, including analysis of variance (ANOVA) (37, 50, 51) and linear regression analysis (38, 47-49). Only one study used multilevel regression models which allowed for consideration of clinic effects in the analyses (43). All studies found evidence for statistically significant differences in HbA1c levels across centres which could not be explained by individual characteristics of children. Studies showed some variation in the selection of case-mix variables that were adjusted for in these analyses. All studies adjusted for basic demographic and disease characteristics that are outside the control of the clinic including individual age, gender, and duration of diabetes.

Results from the DIABAUD2 study showed significant differences in average HbA1c levels between 18 paediatric diabetes centres in Scotland even after controlling for factors related to family structure (49). Four studies (43, 47, 50, 51) found that differences between centres persisted even after adjusting for factors that are within
the control of the clinic, such as type and dose of insulin treatment. For example, the Hvidoere study group analysed glycaemic data of 2,269 adolescents and 1,133 younger children with T1D from different centres in 19 countries across Europe, Japan, Australia and North America and found persistent differences in mean HbA\textsubscript{1c} among centres which could not be explained by patient characteristics and differences in insulin therapy (50, 51). On top of that, differences between centres in the adolescent group were not explained by language difficulties which were used as an indicator of the quality of communication between healthcare professionals and patients or carers (51). Similarly, Hanberger et al. (2008) analysed a large sample of 18,651 children with T1D in Sweden and found significant differences in average HbA\textsubscript{1c} between 20 centres which could not be explained by differences in insulin regimen (47). Gerstl et al. (2008) also found significant differences between 207 diabetes centres in Germany and Austria which persisted even after controlling for the number of insulin injections (43).

Only two population-based studies considered differences in the composition of diabetes centres regarding ethnicity or socioeconomic status. Svennsson et al. (2008) followed a cohort of 2,705 children with T1D over a 10-year period in Denmark and found that differences between clinics remained after adjusting for ethnicity (48). Similarly, significant differences in glycaemic performance between centres in Germany and Austria were observed even after adjustment for differences in socioeconomic status (43).

Four studies (48-51) examined differences between centres in diabetes outcomes other than glycaemic control, including acute diabetes complications (hypoglycaemic and
DKA episodes). Of the above four studies, only one (50) found evidence for significant differences in hypoglycaemic events across centres.

2.3.3 Association between service delivery indicators and diabetes outcomes

Fourteen studies (33-37, 39-46, 52) examined the association between factors involved in service delivery and glycaemic control or other diabetes outcomes (see Table 2). The majority of studies investigated the role of specific indicators of diabetes care including the number of clinic visits, specialist care, health care professionals’ caseload, clinic size, and type of centre.
<table>
<thead>
<tr>
<th>First author (year of publication)</th>
<th>Country (study name/registry)</th>
<th>Sample characteristics</th>
<th>No of clinics</th>
<th>Study period</th>
<th>Design</th>
<th>Outcomes</th>
<th>Statistical analysis</th>
<th>Between Clinic Variation</th>
<th>Case-mix adjustors</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIABAUD2 (2001)</td>
<td>UK – Scotland (DIABAUD2)</td>
<td>1,755 children &lt;15yrs, 94% coverage</td>
<td>18</td>
<td>1997-1999</td>
<td>CS</td>
<td>HbA1c</td>
<td>OLS</td>
<td>Mean HbA1c varied between centres from 8.1% to 10.2% (p&lt;0.001)</td>
<td>Age, gender, diabetes duration, BMI, family history, family structure, season</td>
<td>No adjustment for ethnicity and deprivation</td>
</tr>
<tr>
<td>Danne (2001)</td>
<td>17 countries in Europe, Japan &amp; N.America (HVIDORE)</td>
<td>3,805 children &lt;18 yrs</td>
<td>21</td>
<td>1995, 1998</td>
<td>CS</td>
<td>HbA1c, hypoglycaemic episodes</td>
<td>RMLR, Poison regression</td>
<td>Significant differences in HbA1c between centres (p&lt;0.0001) which persisted in the 2nd sampling period. Differences in HbA1c were also apparent in newly diagnosed children (&lt;3 yrs duration). No significant centre effect in hypoglycaemia (p=0.07)</td>
<td>Age, gender, diabetes duration</td>
<td>Ethnic, cultural and deprivation differences not accounted for</td>
</tr>
<tr>
<td>de Beaufort (2007)</td>
<td>19 countries in Europe, Japan, Australia &amp; N.America (HVIDORE)</td>
<td>2,269 adolescents 11-18 yrs</td>
<td>21</td>
<td>2005</td>
<td>CS</td>
<td>HbA1c, hypoglycaemic &amp; DKA episodes</td>
<td>ANOVA</td>
<td>Significant differences in HbA1c from 7.4% to 9.2% between centres (F=13.61, p&lt;0.001). There were no significant differences in hypoglycaemic or DKA rates.</td>
<td>Age, gender, diabetes duration, insulin regimen and dose, BMI, language difficulties</td>
<td>Language difficulties used as an indicator of the quality in communication between HCP and adolescents/parents</td>
</tr>
<tr>
<td>Hanberger (2008)</td>
<td>Sweden (SWEDIABKIDS)</td>
<td>18,651 children &lt;20 yrs with T1D &gt;1 year Coverage: 20/42 centres</td>
<td>20</td>
<td>2001-2002</td>
<td>CS</td>
<td>HbA1c</td>
<td>OLSR</td>
<td>Mean HbA1c varied between centres from 6.5% to 8.7% (p&lt;0.001)</td>
<td>Age, gender, diabetes duration, insulin dose, number of injections, BMI</td>
<td>No adjustment for ethnicity and deprivation</td>
</tr>
</tbody>
</table>
Table 2. Summary of multi-centre studies providing measures of between-clinic variation in diabetes outcomes for children and young people with Type 1 Diabetes

Notes: CS: cross-sectional, LG: longitudinal, OLSR: Ordinary Least Squares Regression, RMLR: Repeated Measures Linear Regression
Table 2 continued. Summary of multi-centre studies providing measures of between-clinic variation in diabetes outcomes for children and young people with Type 1 Diabetes

<table>
<thead>
<tr>
<th>First author (year of publication)</th>
<th>Country (study name/registry)</th>
<th>Sample characteristics</th>
<th>No of clinics</th>
<th>Study period</th>
<th>Design</th>
<th>Outcomes measured</th>
<th>Statistical analysis</th>
<th>Between Clinic Variation</th>
<th>Case-mix adjustors</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerstl (2008)</td>
<td>Germany &amp; Austria (DPV)</td>
<td>27,035 children &lt;20 yrs coverage ~ 80%</td>
<td>207</td>
<td>1995-2005</td>
<td>CS</td>
<td>HbA1c</td>
<td>Multilevel regression (random effect for clinics)</td>
<td>Mean HbA1c varied between centres from 5.6% to 13.8% (p&lt;0.0001)</td>
<td>Age, gender, diabetes duration, SES, season, treatment period, number of injections</td>
<td>No adjustment for ethnicity No focus on variation</td>
</tr>
<tr>
<td>Svensson (2009)</td>
<td>Denmark (Danish National Diabetes Register)</td>
<td>2,705 children &lt;18 yrs; coverage &gt;99%</td>
<td>19</td>
<td>1996-2006</td>
<td>LG</td>
<td>HbA1c, hypoglycaemic episodes</td>
<td>RMLR</td>
<td>Significant variation in mean HbA1c between centres from 7.8% to 9.1% (p&lt;0.0001)</td>
<td>Age, gender, diabetes duration, ethnicity</td>
<td>No adjustment for deprivation</td>
</tr>
<tr>
<td>O’Hagan (2010)</td>
<td>UK (Wales)</td>
<td>1,689 children &lt;18 yrs; coverage 80-88%</td>
<td>12</td>
<td>2001-2006</td>
<td>LG</td>
<td>HbA1c</td>
<td>ANOVA</td>
<td>Mean HbA1c varied between centres from 8.45% to 10.33% in 2001 and from 8.1% to 9.3% in 2006 (p&lt;0.001)</td>
<td>Age, gender, and weight</td>
<td>No adjustment for ethnicity and deprivation</td>
</tr>
<tr>
<td>de Beaufort (2013)</td>
<td>19 countries in Europe, Japan, Australia &amp; N.America (HVIDORE)</td>
<td>1,133 children &lt;11 yrs with T1D for &gt;1 yr</td>
<td>18</td>
<td>2005</td>
<td>CS</td>
<td>HbA1c, hypoglycaemic &amp; DKA episodes</td>
<td>ANOVA</td>
<td>Mean HbA1c varied significantly between centres from 7.3% to 8.9% (F=22.24, p&lt;0.001). Hypoglycaemic episodes also differed significantly between centres (p&lt;0.001), but there was no difference in DKA rates</td>
<td>Age, gender, diabetes duration, insulin regimen</td>
<td>No adjustment for ethnicity and deprivation</td>
</tr>
</tbody>
</table>

Notes: CS: cross-sectional, LG: longitudinal, RMLR: Repeated Measures Linear Regression
2.3.3.1 Clinic visits

Five studies (34, 39-41, 45) looked at the role of clinic attendance in glycaemic control, and all found a significant association between annual number of clinic visits and HbA$_{1c}$ levels. Most studies support 3 or 4 visits per year as the optimal number related to better glycaemic control, with a less frequent attendance being associated with poorer glycaemic management. Two studies (34, 41) also found that children attending clinic more than five times per year had significantly higher HbA$_{1c}$ levels. As acknowledged by the authors of these two papers, the above results do not imply that higher number of clinic visits lead to poorer glycaemic control, but they rather reflect association rather than causality or indeed possibly reverse causality, i.e. the possibility that children with poor glycaemic management are monitored on a more frequent basis.

2.3.3.2 Specialised care

Although in most studies diabetes care in clinics was delivered by members of the multidisciplinary team, five studies (33, 35, 37, 44, 46) specifically discussed the role of specialised care in the management of children with T1D. Results from a clinical audit in England (33) suggested that children receiving diabetes care from specialised consultants achieved better glycaemic control and had fewer hypoglycaemic episodes compared to children seen by non-specialised consultants. Similarly, clinic-level analysis from a UK-wide audit (35) showed that clinics with specialist paediatricians and clinics in which the diabetes specialist nurse (DSN) worked in both clinical and community settings had better average HbA$_{1c}$ levels.

The role of the DSN was also explored in another study of 1,689 children in Wales (37) which showed that centres which appointed a DSN during a 5-year period had an
improved HbA$_{1c}$ score as opposed to centres with no staffing change. Rosilio et al. (1998) conducted a national survey of 2,579 children across 147 clinics in France and concluded that children served by university hospitals with a higher number of specialised paediatricians and nurses appeared to have better HbA$_{1c}$ levels as opposed to children treated in other hospitals (44). However, no adjustment for potential confounders was considered. Finally, the role of specialist care was examined in another small-scale cross-sectional study in Australia by Hatherly et al. (2011) who found no evidence for association with metabolic outcomes (46).

2.3.3.3 Clinic size

The role of clinic size was investigated in five studies (35, 36, 42-44) providing somewhat conflicting results. Two UK studies (35, 36) found no evidence for an association between clinic size and glycaemic outcomes, but provided inadequate information to judge the robustness of their analyses. A national survey conducted in France (44) explicitly looked at the role of clinic size in HbA$_{1c}$ levels and found that clinics with more than 50 children had a lower crude mean HbA$_{1c}$ indicating better glycaemic performance compared with smaller clinics. Two large-scale studies in Germany and Austria provided conflicting results. Gerstl et al. (2008) found no difference in HbA$_{1c}$ levels between clinics treating more than 50 children as opposed to smaller clinics after controlling for children’s sociodemographic characteristics and insulin treatment (43). Quite surprisingly, Rosenbauer et al. (2012) concluded that, after adjusting for important confounders, children under the care of large centres (>100 patients) had on average poorer glycaemic performance (HbA$_{1c}$ higher by 0.2%) compared with children served by smaller clinics (42).
2.3.3.4  *Staff caseload*

Two UK studies (33, 36) examined the role of nurse and consultant caseload, but neither found evidence for any association with children’s glycaemic control. Another study by the Hvidore study group found no difference in glycaemic control between centres with and without a psychologist (103).

2.3.3.5  *Other indicators of service delivery*

One study (36) utilised a comprehensive measure of service delivery. Harron et al. (2012) used several types of information related to different aspects of service delivery (staffing levels, composition of the multidisciplinary team, education and support provided to children, type of treatment available) to calculate a weighted resource score for each clinic. They found no evidence for a link between resource score and glycaemic control. The role of glycaemic targets set by the diabetes team was discussed in another cross-sectional multi-centre study (52). Swift et al. (2010) analysed glycaemic data from 2,062 adolescents in 21 centres and found that a lower and more consistent HbA1c target set by the members of the diabetes team was associated with improved clinic glycaemic performance (52).
<table>
<thead>
<tr>
<th>First author</th>
<th>Year of publication</th>
<th>Country</th>
<th>Sample characteristics</th>
<th>Design</th>
<th>Outcomes measured</th>
<th>Diabetes service indicators</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baumer</td>
<td>1997</td>
<td>UK (England)</td>
<td>801 CYP in the South Western region of England</td>
<td>Audit</td>
<td>HbA1c, DKA and hypoglycaemic admission rates</td>
<td>Specialist care, nurse caseload</td>
<td>Children receiving care from specialist consultants had better glycaemic control compared to children seen by non-specialists (p&lt;0.001). There was no significant association with nursing caseload (details not reported). Admission rates for hypoglycaemia were at least 3 times higher in children treated by non-specialists as opposed to specialist consultants (p&lt;0.001). There was no difference in DKA admissions. Nursing caseload was not associated with admissions.</td>
<td>Results adjusted for age, diabetes duration, family history, family status, deprivation, and insulin regimen. Differences in laboratory methods for HbA1c across centres</td>
</tr>
<tr>
<td>Dorcy</td>
<td>1997</td>
<td>Belgium</td>
<td>144 children &lt;18yrs with T1D for &gt;5 months followed by the same clinic</td>
<td>LG</td>
<td>HbA1c</td>
<td>Clinic visit</td>
<td>HbA1c was negatively correlated with number of clinic visits (Spearman’s ρ = -2.3, p=0.02)</td>
<td>No adjustment for potential confounders Small sample size</td>
</tr>
<tr>
<td>Jacobson</td>
<td>1997</td>
<td>USA</td>
<td>61 newly diagnosed (duration of T1D &lt;1 yr) children (9-16 yrs) followed for ten years</td>
<td>LG</td>
<td>HbA1c, DKA admission rates</td>
<td>Clinic visits</td>
<td>Children with irregular follow-up (no clinic visit for 1 full year) between years 2-4 had poorer glycaemic control in years 2 (t=2.3, p&lt;0.03) and 3 (t=3.6, p&lt;0.0008) and more episodes of recurrent DKA (χ²=1, p&lt;0.05) compared to children with continuous follow-up (≥1 annual clinic visit). Glycaemic differences disappear in years 7-10.</td>
<td>No adjustment for potential confounders. Vast majority of children were white. Small sample size</td>
</tr>
<tr>
<td>Rosilio</td>
<td>1998</td>
<td>France</td>
<td>2,579 children &lt;19 yrs with T1D for &gt;1 yr across 147 clinics</td>
<td>CS</td>
<td>HbA1c, DKA and hypoglycaemic admission rates</td>
<td>Specialist care, clinic size, type of clinic</td>
<td>Glycaemic control was better in university hospitals with a higher number of specialised paediatricians and nurses (mean HbA1c=8.63%) as compared to other hospitals (mean HbA1c=8.9%) and in clinics with &gt;50 children (mean HbA1c=8.5±1.6%, p&lt;0.0001) as opposed to smaller clinics</td>
<td>National survey (54.4% coverage) No adjustment for potential confounders. Clustering of children within clinics not accounted for in the analysis</td>
</tr>
<tr>
<td>Kaufman</td>
<td>1999</td>
<td>USA</td>
<td>360 (1995), 412 (1996), 442 (1997) children and adolescents followed for 3 yrs</td>
<td>CS</td>
<td>HbA1c</td>
<td>Clinic visits</td>
<td>Children with 3-4 visits per year had significantly better glycaemic control as compared to children with 2 or less annual clinic visits (coefficient= -0.36, p=0.0003). Association of number of visits with HbA1c attenuated after inclusion of adherence and diabetes knowledge in the model (coefficient= -0.3, p=0.04)</td>
<td>Adjustment for individual age and duration</td>
</tr>
</tbody>
</table>
Table 3. Summary of observational studies examining the association between service delivery indicators and diabetes outcomes in children and young people with Type 1 Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>CS: cross-sectional</th>
<th>LG: longitudinal</th>
<th>CYP: children and young people</th>
<th>DKA: diabetic ketoacidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Study 2</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Notes: CS: cross-sectional, LG: longitudinal, CYP: children and young people, DKA: diabetic ketoacidosis
<table>
<thead>
<tr>
<th>First author (year of publication)</th>
<th>Country</th>
<th>Sample</th>
<th>Design</th>
<th>Outcomes measured</th>
<th>Diabetes service indicators</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urbach (2005)</td>
<td>USA</td>
<td>155 children and adolescents &lt;18 yrs</td>
<td>CS</td>
<td>HbA1c</td>
<td>Clinic visits</td>
<td>Children who had 3-4 annual visits (reference group) had better glycaemic control as compared to children attending the clinic less than 2 times (coefficient=0.46, p=0.07) or more than 5 times (coefficient= 1.11, p=0.01)</td>
<td>Adjustment for age, gender, and family status</td>
</tr>
<tr>
<td>Edge (2005)</td>
<td>UK</td>
<td>187 consultants across 169 clinics</td>
<td>Audit</td>
<td>HbA1c</td>
<td>Specialist care, clinic size, DSN</td>
<td>Clinics with specialist paediatricians had better average HbA1c levels (mean HbA1c=8.9%) than clinics with general paediatricians (mean HbA1c=9.4%) –p=0.002. Also, clinics in which the DSN worked in both hospital and community had a better average HbA1c (mean HbA1c=8.9% vs 9.3%, p&lt;0.05)</td>
<td>clinic level analysis analysis based on only about 35% of respondents with both glycaemic and survey data available</td>
</tr>
<tr>
<td>Cardwell (2005)</td>
<td>UK (Northern Ireland)</td>
<td>914 children across 11 clinics</td>
<td>Audit</td>
<td>HbA1c</td>
<td>Clinic visits</td>
<td>Children who attended 4 clinics had better glycaemic control as compared to children attending &lt;4 clinics (coefficient=0.45, 95% CI:0.14-0.7) or &gt;5 clinics (coefficient=0.32, 95% CI:0.03-0.61)</td>
<td>Good ascertainment rate of 97.4% Adjustment for age, gender, and duration of diabetes</td>
</tr>
<tr>
<td>Gerstl (2008)</td>
<td>Germany &amp; Austria</td>
<td>27,035 children across 207 centres</td>
<td>CS</td>
<td>HbA1c</td>
<td>Clinic size</td>
<td>No significant difference in HbA1c between clinics treating &lt;50 and clinics with &lt; 50 patients</td>
<td>Adjustment for age, gender, diabetes duration, SES, season, treatment period, number of injections</td>
</tr>
<tr>
<td>O’Hagan (2010)</td>
<td>UK (Wales)</td>
<td>1,689 Children &lt;18 yrs across 14 clinics followed for five yrs</td>
<td>LG</td>
<td>HbA1c</td>
<td>DSN</td>
<td>In centres which appointed a DSN during the 5-year period, HbA1c improved as opposed to centres with no staffing change (p-value for centre vs time interaction=0.001)</td>
<td>Coverage ranging from 80%-88% Centres which appointed a DSN were those with the highest mean HbA1c (regression to the mean). Adjustment for age, gender, and weight</td>
</tr>
</tbody>
</table>

Notes: CS: cross-sectional, LG: longitudinal, CYP: children and young people, DSN: diabetes specialist nurse
Table 3 continued. Summary of observational studies examining the association between service delivery indicators and diabetes outcomes in children and young people with Type 1 Diabetes

<table>
<thead>
<tr>
<th>First author (year of publication)</th>
<th>Country</th>
<th>Sample</th>
<th>Design</th>
<th>Outcomes measured</th>
<th>Diabetes service indicators</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swift (2010)</td>
<td>19 countries in Europe, Japan, Australia and N. America</td>
<td>2,062 adolescents 11-18 yrs across 21 international centres</td>
<td>CS</td>
<td>HbA1c, Hypoglycaemic and DKA rates</td>
<td>Diabetes team glycaemic targets, psychologist in the team</td>
<td>A lower mean HbA1c target (F=16, df=15, p&lt;0.001) and higher agreement between HCP within centres (F=14.1, df=13, p&lt;0.001) were associated with lower centre HbA1c. Centres with a dietitian had poorer HbA1c (t=4.02, p&lt;0.001). There was no difference in glycaemic control between centres with and without a psychologist</td>
<td>No adjustment for potential confounders</td>
</tr>
<tr>
<td>Hatherly (2011)</td>
<td>Australia</td>
<td>158 children 8-19 yrs</td>
<td>CS</td>
<td>HbA1c</td>
<td>Specialist vs shared care</td>
<td>There was no evidence for an association between the model of care and HbA1c (details not provided)</td>
<td>Adjustment for age, income, location and parental education</td>
</tr>
<tr>
<td>Harron (2012)</td>
<td>UK (Yorkshire &amp; Humber)</td>
<td>2,683 CYP&lt;23 yrs across 21 clinics</td>
<td>CS</td>
<td>HbA1c</td>
<td>Resource score, unit size, nurse and consultant caseload</td>
<td>No significant association between resource score (p=0.41), nurse (p=0.59) or consultant caseload (0.33) and glycaemic control. There was also no evidence for an effect of unit size on HbA1c (details not provided)</td>
<td>Multilevel linear regression Adjusted for age, diabetes duration and deprivation</td>
</tr>
<tr>
<td>Rosenbauer (2012)</td>
<td>Germany &amp; Austria</td>
<td>30,708 children and adolescents across 305 centres</td>
<td>LG</td>
<td>HbA1c</td>
<td>Clinic size, type of centre (general, rehabilitation)</td>
<td>Patients treated in larger centres (&gt;100 patients) had on average higher HbA1c levels (p&lt;0.02). there was no difference in HbA1c between different types of diabetes centres</td>
<td>Adjusted for age, gender, duration, migration status, BMI, insulin regimen and dose Mixed model with centre as a random effect</td>
</tr>
</tbody>
</table>

Notes: CS: cross-sectional, LG: longitudinal, CYP: children and young people, DKA: diabetic ketoacidosis
2.4 Discussion

The findings of the current review provide consistent evidence from large multi-centre, observational studies for significant differences in glycaemic control between clinics treating children with T1D. These differences persisted even after correcting for basic demographics and disease profile of children attending clinics. Taken together the above findings indicate that clinic factors might contribute to these unexplained differences between clinics. Clinic differences in HbA1c also persisted even after controlling for factors within the control of the clinic, such as type and intensity of insulin regimen. This suggests that aspects of diabetes care other than insulin regimens on offer might explain how clinics contribute to differences in children’s metabolic control.

The second part of the current review aimed to provide an insight into the specific clinic-level factors which might account for some of the observed differences between clinics. There was some evidence provided by observational studies and clinical audits suggesting an association of more frequent clinic attendance and provision of specialist care with diabetes better outcomes and especially glycaemic control. However, the role of other indicators of service delivery, including clinic size, caseload and staffing levels was not straightforward, and results were rather conflicting.

A striking example is that of the association between clinic size and glycaemic performance. While it could be hypothesised that centralisation of diabetes clinics into larger centres may provide more opportunities for specialised care, which in turn could be linked to improved glycaemic outcomes, results of the current review did not
provide support for this hypothesis. Included studies showed quite divergent results which might reflect methodological differences in the way clinic size is treated (e.g. as a continuous or binary variable with different cut-offs). In any case, even in studies that found evidence for glycaemic differences related to unit size, the magnitude of these differences was small and therefore of limited clinical significance.

The findings of the review should be interpreted with some caution since there are important limitations to be considered. Firstly, multi-centre studies reporting on between-clinic differences have not taken into account relevant factors, exogenous to the clinic environment, which are known to be associated with glycaemic control. For example, in most of these studies, little consideration has been given to imbalances in the distribution of socioeconomic or ethnicity profiles of children across clinics. The apparent differences between clinics might be artefacts of the differential composition of clinics, as, for example, a clinic with poor glycaemic performance could be the result of the clinic having a large number of highly deprived children. It might be the case that after controlling for differences in deprivation or other indicators of socioeconomic status, some of the differences between clinics will be explained. Other important determinants of glycaemic control which might act as confounders include measures of adiposity (e.g. BMI), family coherence and support, parental education, and lifestyle behaviours.

A second limitation is related to the type of statistical analysis used by the included studies. All of the existing studies have inadequately addressed the role of clinic context in glycaemic control by either employing traditional modelling techniques operating only at the individual level or by treating clinic variation as a statistical issue of no substantive interest. Variation in diabetes outcomes should incorporate the
contribution of both clinic context and individual composition and failure to acknowledge these sources of variation might lead to biased estimates (32).

Another major obstacle to effective policy action regarding clinic variation, as explored in studies identified by the current review, is that it is typically conceptualised as absolute differences between clinic means. In addition to that, we need to consider the share of the total variation in the glycaemic control that exists between clinics (53, 54). This idea corresponds to the concept of clustering (55). Understanding how glycaemic outcomes are geographically clustered across clinics within a country is of crucial importance for policy development and implementation (56). This is particularly important when available resources are limited and need to be allocated most efficiently. For example, if glycaemic outcomes are heterogeneously distributed across clinics (high clustering), then policies aiming to reduce centre variation by targeting low performing clinics will see most resources being efficiently delivered to areas at the highest need because they will capture most poorly controlled children in the country. On the other hand, if children’s metabolic control is uniformly achieved across clinics in such a way that there is considerable overlap between clinics’ distributions (low clustering), then policies aiming to reduce centre variation by targeting low performing clinics may narrowly miss most poorly controlled children in the country. The concept of clustering and its relevance to health policy development is illustrated in Figure 4.
Figure 4. Graphic illustration of the role of clustering in the development of clinic-based policy interventions in type 1 diabetes.

2.4.1 Conclusion

Overall, the current systematic review provides consistent evidence for important differences between clinics in glycaemic outcomes for children with T1D. These findings imply that clinic context might play an important role in shaping diabetes outcomes; however, existing studies thus far have inappropriately focused on looking at absolute differences between clinic means which can be misleading in guiding policy action. Findings of the current review provided limited insight into which aspects of service delivery can explain the observed differences between clinics. Most of the evidence is also based on clinical audits and small-scale, cross-sectional studies with methodological flaws. Association between diabetes care and outcomes is not straightforward, and future research should look at these complex interactions between
different aspects of service delivery using a statistically and methodologically robust approach.

2.5 Update of the systematic review

An update of the review was conducted using the same search terms. Embase, and Medline were searched between June 2015 and December 2017. Five hundred and thirty four unique citations were identified, none of which was eligible for inclusion in the review. One study explored variations in HbA$_1c$ and rates of hypoglycaemia across 16 federal states of Germany rather than across paediatric diabetes centres and was not eligible for inclusion in the review (57).
Chapter 3  A systematic review and meta-analysis on the effectiveness of UK-based psycho-educational interventions for children and young people with type 1 diabetes

3.1 Introduction

Children and young people with T1D in the UK are typically managed by multidisciplinary teams in hospital-based paediatric diabetes units. Even though administration of insulin and dietary changes constitute the main components of diabetes management for children and young people, the need for diabetes education programs has been recognised as a priority by governmental bodies and many organisations (58-60). This is unsurprising given that such programs are essential in integrating the multifaceted difficulties of diabetes management into everyday life.

Two main types of programs are available: traditional educational programs which aim to enhance knowledge and skills related to diabetes, and programs that have a psychological component and aim to support coping strategies, stress management, problem-solving, goal-setting, empowerment, and counselling. Although educational programs, with or without psychological components, have been successfully introduced for adults with T1D across the UK (61, 62), there is a surprising lack of an evidence-base for similar programs for the paediatric population (63).

The effectiveness of psycho-educational programs on glycaemic control and psychological functioning in children and young people with T1D has been examined in several systematic reviews over the last few years. In a commissioned review by the
NHS Health Technology Assessment programme in 2001, Hampson et al. made the first attempt to systematically review existing evidence on the effectiveness of such interventions in adolescents (64). Hampson et al. summarised intervention effects by calculating the standardised mean difference (SMD), which represents the difference in mean change-from-baseline scores between groups divided by the standard deviation of change scores. They found that psycho-educational interventions had a non-significant effect on children’s glycaemic control (equivalent to a decrease of 0.6% in levels of HbA1c; SMD=0.3, 95% CI -0.04 to 0.7), but conferred significant improvements in psychological functioning (SMD=0.4, 95% CI 0.2 to 0.6) (64). The review also concluded that existing evidence was mostly from the US with a notable scarcity of UK-based randomised controlled trials (RCTs). Five years later, Murphy et al. conducted an updated review which showed little progress in the development of new UK interventions (29). Two later meta-analyses provided evidence for a glycaemic benefit of such interventions. The first showed that, compared to controls, children receiving a psychological intervention had lower HbA1c (SMD = -0.35, 95% CI -0.66 to -0.04) and psychological distress (SMD = -0.5, 95% CI: -0.8 to -0.1) (65). The second meta-analysis found that family-based psycho-educational interventions conferred improvements in both levels of HbA1c (mean difference in % HbA1c = -0.6, 95% CI -1.2 to -0.1) and diabetes-related knowledge (SMD= 0.94, 95% CI 0.67 to 1.82) (66).

The evidence for the effectiveness of psycho-educational interventions in children with T1D is predominantly based on non-UK trials. Only two, small UK RCTs were included in previous reviews (67, 68). Of these two, the most recent was published back in 2002 (67). However, the evidence for the effectiveness of such interventions might depend on the context within which they are implemented. For example, the
content and quality of standard care (against which interventions are compared) varies considerably across countries (69). This variation implies that it is unclear whether conclusions from earlier reviews can be extrapolated to the UK. Additionally, several large UK RCTs of psycho-educational interventions have been developed over the last decade but have not been systematically reviewed. Hence, there is a need for a systematic evaluation of these interventions to examine whether the evidence for the effectiveness of UK-based psycho-educational interventions is sufficient to support adoption of such interventions in the UK.

3.1.1 Aim of the systematic review

The aim of this chapter is to critically appraise and synthesise existing evidence from UK-based RCTs on the effectiveness of psycho-educational interventions in improving glycaemic control, psychosocial functioning, diabetes knowledge and other outcomes in CYP with T1D.

3.2 Methods

The current systematic review was conducted in line with the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) guidelines (70). The protocol of this review was published in the International Prospective Register for Systematic Reviews (PROSPERO) - Registration No: CRD42015010701.

3.2.1 Search strategy

Six databases were searched for citations published up to March 2016. These included Medline, Embase, Cochrane, PsycINFO, CINAHL, and Web of Science. A
combination of free-text words and medical subject heading (MeSH) terms were used to create five subsets of citations relating to population, intervention, outcomes of interest, randomised controlled trials and studies conducted in the UK. Results were limited to CYP up to 24 years. No limitation was imposed on language or year of publication. The search strategy used in Medline is presented in Table 4. A similar search strategy was followed in other databases. A number of “snowballing” techniques were also used to increase the sensitivity of the searches, including hand-searching reference lists, and contacting corresponding authors of selected articles for published or unpublished relevant trials.

3.2.2 Inclusion and exclusion criteria

Psycho-educational interventions were defined as any intervention targeting CYP, their carers/families and/or health care professionals which aimed to improve diabetes management in children by providing knowledge or skills or any form of psychological training or support. Studies were not excluded based on setting, mode of delivery or length of the intervention. Included trials had to be conducted in the UK and examine the effectiveness of the educational or psycho-educational intervention in CYP up to 24 years diagnosed with T1D. Eligible interventions were randomised controlled trials that included a non-intervention arm of children receiving standard care. Interventions in which the control group was matched for the extra contact time (i.e. attention control) were included. Trials which combined type 1 and type 2 diabetes or children and young people up to 24 years old with adults (24 years and above) were excluded except if findings were presented separately by type of diabetes or age. Letters to the editor, commentaries, editorials, reviews, conference proceedings, intervention
development protocols, feasibility/pilot trials and qualitative studies were also excluded.

**Table 4. Search strategy (Medline via Ovid)**

<table>
<thead>
<tr>
<th>Search terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ((&quot;type 1&quot; or &quot;type I&quot; or paediatric or paediatric or child* or young or youth* or juvenil* or (insulin adj depend*) or insulin-depend* or adolesc* or teen*) adj4 (diabet* or DM)).mp.</td>
</tr>
<tr>
<td>2. (T1DM or DM1 or T1D or IDDM).mp.</td>
</tr>
<tr>
<td>3. exp Diabetes Mellitus, Type 1/</td>
</tr>
<tr>
<td>4. or/1-3</td>
</tr>
<tr>
<td>5. (educat* or information or learn* or teach* or self-care or psycho* or counsel* or motivation* or famil* or parent*).mp.</td>
</tr>
<tr>
<td>6. ((&quot;problem-solving&quot; or cognitive or behavio* or CBT) adj4 (therap* or interv* or program* or train*)).mp.</td>
</tr>
<tr>
<td>7. Health Education/ or Psychotherapy/ or Cognitive Therapy/ or Behavior Therapy/</td>
</tr>
<tr>
<td>8. or/5-7</td>
</tr>
<tr>
<td>9. ((glycaemic or glycemic or metabolic or diabet* or glucose) adj4 (control or management or outcome* or level*)).mp.</td>
</tr>
<tr>
<td>10. (HbA1c or A1c or &quot;HbA(1c)&quot;).mp.</td>
</tr>
<tr>
<td>11. ((insulin adj4 (use or injection* or dose*)).mp.</td>
</tr>
<tr>
<td>12. (Hypoglyc* or ketoacidosis or ketosis or DKA).mp.</td>
</tr>
<tr>
<td>13. (adher* or knowledge* or skill* or &quot;insulin sensitivity&quot; or behavi* or &quot;quality of life&quot; or manage* or self-management or control* or self-efficacy or diet* or eating or nutrition* or exerci* or regime).mp.</td>
</tr>
<tr>
<td>14. Haemoglobin A, Glycosylated/</td>
</tr>
<tr>
<td>15. Insulin resistance/</td>
</tr>
<tr>
<td>16. Quality of Life/</td>
</tr>
<tr>
<td>17. Health Behavior/</td>
</tr>
<tr>
<td>18. or/9-17</td>
</tr>
<tr>
<td>19. Randomised Controlled Trials as Topic/ or randomised controlled trial/ or Random Allocation/ or Double Blind Method/ or Single Blind Method/ or clinical trial/ or exp Clinical Trials as topic/or PLACEBOS/</td>
</tr>
<tr>
<td>20. clinical trial, phase i.pt or clinical trial, phase ii.pt or clinical trial, phase iii.pt or clinical trial, phase iv.pt or controlled clinical trial.pt or randomised controlled trial.pt or multicentre study.pt or clinical trial.pt</td>
</tr>
<tr>
<td>21. or/19-20</td>
</tr>
<tr>
<td>22. (clinical adj trial$).tw</td>
</tr>
<tr>
<td>23. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw</td>
</tr>
<tr>
<td>24. placebo$tw or randomly allocated.tw</td>
</tr>
<tr>
<td>25. (allocated adj2 random$).tw</td>
</tr>
<tr>
<td>26. or/22-25</td>
</tr>
<tr>
<td>27. 21 or 26</td>
</tr>
<tr>
<td>28. case report.tw</td>
</tr>
<tr>
<td>29. letter/ or historical article/</td>
</tr>
<tr>
<td>30. or/28-29</td>
</tr>
<tr>
<td>31. 27 not 30</td>
</tr>
<tr>
<td>32. exp Great Britain/ or (Britain or british or Ireland or Irish or wales or welsh or Scottish or scots or Scotland or England or English or Birmingham or leeds or London or Liverpool or Manchester or Glasgow or Edinburgh or Cardiff or Belfast or Oxford or Cambridge or &quot;United Kingdom&quot; or UK or GB or aberdeen).ti,ab,in,cp,hw</td>
</tr>
<tr>
<td>33. 4 AND 8 AND 18 AND 31 AND 32</td>
</tr>
<tr>
<td>34. limit 33 to (&quot;all child (0 to 18 years)&quot; or &quot;young adult (19 to 24 years&quot;) and humans)</td>
</tr>
</tbody>
</table>
3.2.3 Types of outcome measures

Glycaemic control, as measured by HbA1c levels, was the primary outcome. Secondary outcomes included indicators of psychosocial functioning, diabetes-related knowledge, dose and frequency of insulin treatment, adverse events (episodes of hypoglycaemia and diabetic ketoacidosis-DKA), and service utilisation.

3.2.4 Study selection

Retrieved citations were entered into EndNote. After removal of duplicate citations, titles and abstracts of unique citations were screened against the eligibility criteria. Full papers of potentially eligible articles were retrieved and further screened. Interventions were categorised according to their primary aims as educational (i.e. those targeting diabetes-related knowledge and skills), psychological (i.e. those providing psychosocial support) or psycho-educational (those combining educational with psychological components). Psycho-educational interventions were categorised into five subgroups: supportive or counselling therapy (comprising motivational interviewing, non-directive counselling, and solution-focused therapy); cognitive behavioural therapy (using methods such as problem solving, goal setting, activity scheduling, cognitive restructuring, and stress management); family systems therapy; psychotherapy (including psychodynamic or interpersonal approaches) and other interventions (such as those employing eclectic approaches). The above groups were selected as they represent conceptually similar psychological approaches.
3.2.5 Data extraction

A pre-piloted data extraction form was used to extract data from eligible trials as per guidelines by the Centre for Review and Dissemination (CRD) for systematic reviews in healthcare (71). The following data were extracted: study design and methodology, intervention characteristics and type of care received by controls, baseline characteristics, sample size and power of the study, recruitment and study completion rates, reasons for attrition, baseline and follow-up outcome data for each trial arm, and information for assessment of the risk of bias. If there was insufficient information on trial methods or data, corresponding authors of included papers were contacted by email; three authors were contacted, and all provided additional information.

3.2.6 Risk of bias assessment

Quality of included RCTs was evaluated using the Cochrane Collaboration’s tool for assessing the risk of bias (72). The following domains were used for the assessment: sequence generation; allocation concealment; blinding of outcome assessors; completeness of outcome data; selective reporting of outcomes; and other sources of bias. The domain related to blinding of participants and personnel to the knowledge of the intervention was excluded from the assessment as this was not possible in the context of psycho-educational interventions. For each of the six domains, trials were classified as being at low, high, or unclear risk of bias. Assessment of the domains relating to the blinding of outcome assessors and data completeness was conducted separately for glycaemic and psycho-educational outcomes.
3.2.7 Data synthesis

Data were analysed narratively and via meta-analysis. The SMD was used to summarise intervention effects on continuous outcomes. SMD was calculated by dividing the between-group difference in mean change-from-baseline scores (or follow-up scores adjusted for baseline values) by the pooled standard deviation of the change scores (73). Calculation of the intervention effect was based on the follow-up interval set a priori for the definition of the primary outcome. Four trials provided multiple follow-up measurements without stating any primary time point, in which case the longest available follow-up measurement was chosen. If the standard deviation of the change scores was not reported in the published paper, it was obtained by correspondence with the authors, or by hand calculating from available reported data. For seven studies none of the above was possible, and standard deviations of change scores were imputed using the standard deviation of baseline and follow-up measurements and assuming a conservative correlation coefficient of 0.5 between the two measurements (74). The assumed correlation of r=0.5 varied from r=0.3 to r=0.7 to examine if this had an impact on the summary estimates; results were found to be robust to these variations.

Each study contributed only one estimate per psychosocial construct in order to avoid unit of analysis errors. For instance, if studies reported both patient and parent/carer reports of the same measure, the former were used in the meta-analysis. In addition, if studies reported multiple comparisons for different groups (e.g. for younger and older children), these measures were combined within each study before being entered in the meta-analysis. If comparisons were not independent of one another (for example if trials reported several dimensions of quality of life for the same children), a synthetic
effect size for each study was calculated. This was defined as the weighted mean of the multiple effects with a variance that is adjusted for the correlation between the outcomes (75), assuming it to be r=0.5 if not stated. In RCTs with multiple intervention arms, the intervention arm which was directly comparable to the control arm (i.e. the arm without any co-intervention or change in routine care) was chosen. In the case of cluster-randomised trials, effect sizes were adjusted for clustering effect and baseline values, or if not available, sample sizes were adjusted for the “design effect” (73). In cross-over trials, data from the first period were used.

3.2.8 Overall summary effects

Effect sizes from individual trials were statistically combined using a random effects model to take into consideration between-study differences in the interventions and settings. Findings were reported as pooled SMD with 95% confidence intervals. An SMD of ~0.2, ~0.5, and ~0.8 was considered as small, medium and large respectively (76). To aid clinical interpretation of intervention effects on HbA1c pooled SMD were re-expressed as absolute units by multiplying the estimate by the pooled standard deviation of included trials. Finally, forest plots were generated to assess intervention effects across studies visually. Stata 12 (StataCorp, College Station, Texas) was used for all analyses.

3.2.9 Assessment of heterogeneity

I^2 statistic was used to assess between-study heterogeneity. I^2 statistic quantifies the proportion of total variation that can be attributed to heterogeneity (77, 78). Values of I^2 ≤50%, 50-75%, and ≥75% were considered indicative of low, moderate and high heterogeneity respectively (77). Individual studies were removed one at a time from
the meta-analysis to examine whether heterogeneity could be explained. Where possible, subgroup analyses were conducted against possible modifying factors (i.e. quality of trial, type of intervention, and age) to investigate potential sources of heterogeneity.

3.2.10 Publication bias

A funnel plot for the primary outcome was generated to evaluate the possibility of publication bias.

3.2.11 Sensitivity analyses

To explore whether findings were robust to the selection of time point, meta-analyses were repeated, where possible, by including the shortest follow-up measurement (i.e. the measurement that was available immediately after the end of the intervention); no differences were observed in the summary estimates.

3.3 Results

The search strategy found 1,189 potentially relevant papers, of which 74 were read in full. Two more articles were identified from reference lists. In total, eleven studies (67, 68, 79-86) representing ten RCTs met the eligibility criteria and were included in the current review (see Figure 5).
Figure 5. Flow diagram of study selection
3.3.1 Description of included trials

Characteristics of included RCTs are shown in Table 5. Sample size of trials ranged from 48 to 693 with a median of 113. Overall, rates of participation (i.e. participants recruited as a proportion of eligible participants) were low and ranged from 31% to 70.2%, with a median of 50%. Six RCTs recruited only adolescents (67, 79, 81, 82, 84, 85) one of which also included young people 24 years or younger (67). All but three trials (67, 68, 82) targeted children who had been diagnosed with T1D for more than one year. The median duration of diabetes was 5.6 years (range 2.8 to 9.2 years). In all RCTs, participants were analysed by intention to treat. Six trials had a parallel group design (67, 79, 81-84), one trial had a cross-over design (68), and three were cluster-randomised (80, 85, 86). Results from the critical appraisal of included trials are shown in Table 6.

Of the ten RCTs, seven (67, 79, 80, 82-84, 86) used psycho-educational and three (68, 81, 85) purely educational interventions. All psycho-educational interventions reported employing an underlying theoretical model. Of the seven psycho-educational interventions, three employed supportive or counselling therapy (79, 80, 83), two used cognitive behaviour therapy (67, 82), one used family therapy (84), and one (86) used an eclectic approach. Six trials (80-84, 86) provided a reference to the full trial protocol. However, only four trials (80, 83-85) described the intervention in sufficient detail to be replicated in practice. In all trials, control groups received standard care which in most cases included three to five clinic visits per year; however, in one trial (79) the control group was matched for contact time by receiving extra support visits. Only one trial (80) described standard care in detail.
Interventions targeted individual children (67, 79, 83, 86), groups of children (85), family groups (68, 80, 81, 84), and parents (82). Four interventions (80, 81, 84, 86) were delivered in clinics and six (67, 68, 79, 82, 83, 85) in home or other community settings. The intensity of interventions differed substantially; the total time spent on intervention ranged from 2.4 to 35 hours with a median value of 8.5 hours. Dietitians and nurses delivered most interventions, and in one trial (79) the interventionist had a background in psychology. Half of the trials (67, 80, 84-86) provided some evidence for the training of the interventionist.
Table 5. Characteristics of included trials

<table>
<thead>
<tr>
<th>First author (publication year)</th>
<th>Country (study name)</th>
<th>No of participants randomised (eligibility criteria)</th>
<th>Mean (SD) % HbA1c at baseline</th>
<th>Mean (SD or range) duration of diabetes (years)</th>
<th>Intervention, setting, mode of delivery</th>
<th>Theoretical Model</th>
<th>Control group</th>
<th>Interventionist</th>
<th>Duration of intervention in months (except as noted)</th>
<th>Assessmen points * (months)</th>
<th>Time in min spent on each session (No of sessions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloomfield (1990)</td>
<td>Scotland</td>
<td>48 (children &lt;13 years with T1D &gt; 3 months)</td>
<td>9.3 (1.5)</td>
<td>2.8 (2.1)</td>
<td>9.0 (3.0)</td>
<td>Semi-structured educational program, Community, Group of families</td>
<td>-</td>
<td>Usual care</td>
<td>D</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Howells (2002)</td>
<td>Scotland</td>
<td>79 (children 12-24 years)</td>
<td>8.8 (1.7)</td>
<td>7.0 (4.5)</td>
<td>16.8 (3.4)</td>
<td>Negotiated telephone support, Home, Child</td>
<td>SLT</td>
<td>Usual care</td>
<td>D</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Franklin (2006)</td>
<td>Scotland (Sweet Talk)</td>
<td>64 (children 8-18 years with T1D &gt;1 year)</td>
<td>10.2 (1.7)</td>
<td>4.1 (1.7 - 8.6)</td>
<td>13.5 (10.5-15.6)</td>
<td>Automated text message support plus goal-setting education, Home, Child</td>
<td>SCT</td>
<td>Usual care</td>
<td>MDT</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Channon (2007)</td>
<td>Wales</td>
<td>80 (adolescents 14-17 years with T1D &gt;1 year)</td>
<td>9.2 (1.9)</td>
<td>9.2 (1.8)</td>
<td>15.3 (1.1)</td>
<td>Motivational interviewing, Home &amp; community, Child</td>
<td>MSA</td>
<td>Usual care plus additional support visits</td>
<td>PSY + N</td>
<td>12</td>
<td>6, 12, 24</td>
</tr>
<tr>
<td>Murphy (2012)</td>
<td>UK (FACTS)</td>
<td>305 (adolescents with T1D &gt;1 year)</td>
<td>9.3 (1.9)</td>
<td>5.6 (3.4)</td>
<td>13.2 (2.0)</td>
<td>Family-centered structured program, Clinic, Group of families</td>
<td>SLT</td>
<td>Usual care</td>
<td>MDT</td>
<td>6</td>
<td>9, 12, 18</td>
</tr>
<tr>
<td>Robling (2012)</td>
<td>UK (DEPICTED)</td>
<td>693 (children 4-15 years with T1D &gt;1 year)</td>
<td>9.3 (1.8)</td>
<td>5.1 (2.7)</td>
<td>10.6 (2.8)</td>
<td>Training healthcare practitioners in consultation skills using eclectic approach, Clinic, Child with carer</td>
<td>CMCS</td>
<td>Usual care</td>
<td>MDT</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>


* from the start of the intervention
### Table 5 continued. Characteristics of included trials

<table>
<thead>
<tr>
<th>First author (publication year)</th>
<th>Country (study name)</th>
<th>No of participants randomised (eligibility criteria)</th>
<th>Mean (SD) % HbA₁c at baseline</th>
<th>Mean (SD) or range duration of diabetes (years)</th>
<th>Intervention, setting, mode of delivery</th>
<th>Theoretic al Model</th>
<th>Control group</th>
<th>Interventionist</th>
<th>Duration of intervention in months (except as noted)</th>
<th>Assessmen t points *</th>
<th>Time in min spent on each session (No of sessions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coates (2013)</td>
<td>N. Ireland (CHOICE)</td>
<td>135 (adolescents 13-19 years with T1D &gt;1 year)</td>
<td>8.9 (1.5)</td>
<td>6.6 (3.8)</td>
<td>15.4 (1.8)</td>
<td>Structured educational program, Clinic, Group of families</td>
<td>-</td>
<td>Usual care</td>
<td>N + D</td>
<td>5</td>
<td>1, 3, 6, 12, 24</td>
</tr>
<tr>
<td>Doherty (2013)</td>
<td>UK (Triple P)</td>
<td>90 (Parents of adolescents aged 11-17 years)</td>
<td>8.5 (1.3)</td>
<td>5.1 (3.4)</td>
<td>13.5 (1.0)</td>
<td>Self-directed, web-based behavioural intervention, Home, Parents</td>
<td>SLT</td>
<td>Usual care</td>
<td>NA</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Christie (2014)</td>
<td>England (CASCADE)</td>
<td>365 (Children 8-16 years with T1D &gt;1 year &amp; HbA₁c ≥ 8.5%)</td>
<td>10.0 (1.5)</td>
<td>5.9 (3.3)</td>
<td>13.2 (2.1)</td>
<td>Motivational interviewing, solution-focused brief therapy, Clinic, Group of families</td>
<td>MSA</td>
<td>Usual care</td>
<td>N + O</td>
<td>4</td>
<td>12, 24</td>
</tr>
<tr>
<td>Price (2016)</td>
<td>UK (KICK-OFF)</td>
<td>480 (adolescents 11-16 years with T1D &gt;1 year)</td>
<td>9.2 (1.7)</td>
<td>5.6 (2.0)</td>
<td>13.8 (1.5)</td>
<td>Intensive, structured education course, Community, Group of children</td>
<td>-</td>
<td>Usual care</td>
<td>N + D + O</td>
<td>5 days</td>
<td>6, 12, 24</td>
</tr>
</tbody>
</table>


* from the start of the intervention.
Table 6. Critical appraisal of RCTs included in the systematic review

<table>
<thead>
<tr>
<th>First author (publication year)</th>
<th>Participation rate$^a$</th>
<th>Type of analysis</th>
<th>Statistician blinded?</th>
<th>Retention rate $^b$ in each arm (CG/ IG)</th>
<th>Reasons for attrition explicitly reported</th>
<th>Groups similar at baseline?</th>
<th>Sample size large enough to detect a meaningful effect if it had existed?</th>
<th>Intervention sufficiently described to be replicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloomfield (1990)</td>
<td>52%</td>
<td>ITT</td>
<td>NR</td>
<td>100% / 100%</td>
<td>NA</td>
<td>Y</td>
<td>? $^d$</td>
<td>N</td>
</tr>
<tr>
<td>Howells (2002)</td>
<td>65%</td>
<td>ITT$^i$</td>
<td>NR</td>
<td>90.3% / 83.9%</td>
<td>Y</td>
<td>Y</td>
<td>Y $^e$</td>
<td>N</td>
</tr>
<tr>
<td>Franklin (2006)</td>
<td>70%</td>
<td>ITT$^i$</td>
<td>NR</td>
<td>96.4% / 96.7%</td>
<td>Y</td>
<td>Y</td>
<td>N $^f$</td>
<td>Y</td>
</tr>
<tr>
<td>Channon (2007)</td>
<td>47%</td>
<td>ITT$^i$</td>
<td>NR</td>
<td>54% / 69.8%</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Murphy (2012)</td>
<td>37%</td>
<td>ITT$^i$</td>
<td>NR</td>
<td>95.9% / 97.5%</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Robling (2012)</td>
<td>55%</td>
<td>ITT$^i$</td>
<td>NR</td>
<td>95.2% / 95.3%</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Coates (2013)</td>
<td>34%</td>
<td>ITT</td>
<td>NR</td>
<td>43.1% / 44.3%</td>
<td>N</td>
<td>?</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Doherty (2013)</td>
<td>NA $^j$</td>
<td>ITT$^i$</td>
<td>NR</td>
<td>69.6% / 50%</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Christie (2014)</td>
<td>31%</td>
<td>ITT$^i$</td>
<td>NR</td>
<td>81.4% / 74.2%</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Price (2016)</td>
<td>27%</td>
<td>ITT$^i$</td>
<td>NR</td>
<td>82.4% / 72.5%</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
</tbody>
</table>

Notes: ITT: Intention-to-treat. Y: Yes; N: No; NR: Non-Reported. NA: not applicable. ?: unclear
$^a$ % of eligible participants contacted recruited; $^b$ % of those randomised completing study (it refers to the primary outcome measured at the longest interval); $^c$ judgement reached by reviewers after consideration of attendance information and trial authors’ interpretation in the manuscript; $^d$ no power calculations made; $^e$ adequate power for psychological outcomes but not for HbA$_1c$; $^f$ an unreasonably high difference in HbA$_1c$ was assumed for power calculations (1.7%); $^g$ non-white children; $^h$ children with HbA$_1c$ < 8.5%; $^i$ only patients in whom the outcomes were measured have been included in the analysis; $^j$ web-based trial
Table 6 continued. Critical appraisal of RCTs included in the systematic review

<table>
<thead>
<tr>
<th>First author (publication year)</th>
<th>Reference to full trial protocol</th>
<th>Have important populations been excluded?</th>
<th>Intervention delivered as planned?</th>
<th>Evidence for training of interventionist?</th>
<th>Was adherence to the protocol monitored?</th>
<th>Attendance</th>
<th>Was attendance sufficient to demonstrate effect a?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloomfield (1990)</td>
<td>N</td>
<td>N</td>
<td>NR</td>
<td>N</td>
<td>NR</td>
<td>Attendance rate &gt;80%</td>
<td>Y</td>
</tr>
<tr>
<td>Howells (2002)</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Each participant received an average number of 16 phone calls</td>
<td>Y</td>
</tr>
<tr>
<td>Franklin (2006)</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>NR</td>
<td>NA</td>
<td>Y</td>
</tr>
<tr>
<td>Murphy (2012)</td>
<td>Y</td>
<td>N</td>
<td>?</td>
<td>Y</td>
<td>NR</td>
<td>50% of participants attended ≥ 4/6 sessions, 30% attended none</td>
<td>N</td>
</tr>
<tr>
<td>Robling (2012)</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Intervention incorporated into routine clinical care</td>
<td>Y</td>
</tr>
<tr>
<td>Coates (2013)</td>
<td>Y</td>
<td>?</td>
<td>?</td>
<td>N</td>
<td>NR</td>
<td>94% of participant completed training</td>
<td>Y</td>
</tr>
<tr>
<td>Doherty (2013)</td>
<td>Y</td>
<td>?</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>participants completed an average of 6.5/10 modules</td>
<td>N</td>
</tr>
<tr>
<td>Christie (2014)</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
<td>Y</td>
<td>Y</td>
<td>37% of families did not attend any module</td>
<td>N</td>
</tr>
<tr>
<td>Price (2016)</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>29 out of 995 course days (3%) missed</td>
<td>Y</td>
</tr>
</tbody>
</table>

Notes: ITT: Intention-to-treat, Y: Yes, N: No, NR: Non-Reported, NA: not applicable, ?: unclear

a % of eligible participants contacted recruited; b % of those randomised completing study (it refers to the primary outcome measured at the longest interval); c judgement reached by reviewers after consideration of attendance information and trial authors’ interpretation in the manuscript; d no power calculations made; e adequate power for psychological outcomes but not for HbA1c; f an unreasonably high difference in HbA1c was assumed for power calculations (1.7%); g non-white children; h children with HbA1c < 8.5%; i only patients in whom the outcomes were measured have been included in the analysis; j web-based trial
Five interventions (67, 68, 79, 83, 86) lasted for one year with the remaining interventions (80-82, 84, 85) having a duration of up to 6 months. Half of the trials had a follow-up assessment after the end of the intervention. Retention rates ranged from 43% to 100%. Half of the included studies (68, 79, 81-83) were considered underpowered to detect an effect in their primary outcome. Six trials reported monitoring adherence to trial protocol (67, 79, 80, 82, 85, 86). Eight trials (67, 68, 80-82, 84-86) provided information on intervention attendance and in three of them (80, 82, 84) attendance rates were deemed as insufficient to demonstrate an intervention effect.

### 3.3.2 Risk of bias

Half of the included trials had an unclear risk of selection bias due to inadequate sequence generation (68, 79-81, 86) because the authors did not report the randomisation method. Risk of bias due to inadequate allocation concealment could not be assessed in four trials (68, 80, 83, 84). Even though blinding of participants and interventionists is not possible in such interventions, the risk of detection bias from outcome assessment was considered small for HbA1c (objectively measured) and for most of the psycho-educational outcomes (use of standardised scales). In three trials (79, 82, 84) there was a high risk of bias due to incomplete psychological data, which reflected the high attrition rate in this type of interventions. Five trials (68, 79, 81, 85, 86) carried a high risk of selective outcome reporting as they did not report all psychological outcomes. Other sources of bias included inappropriate study design.
(cross-over design prone to carryover effects) (68), and baseline imbalances not taken into account in the analyses (82). When all bias domains were considered together, one study (68) had low risk in only one domain, three studies (79, 81, 84) scored low risk in two or three domains, and the remaining trials (67, 80, 82, 83, 85, 86) had low risk in four or more bias categories. A detailed description of the assessment of risk of bias is presented in Table 7 and Figure 6.
Figure 6. Outcome of risk of bias assessment by type of bias

Note: PEO=psycho-educational outcomes
Table 7. Outcomes of risk of bias assessment by trial

<table>
<thead>
<tr>
<th>First author (publication year)</th>
<th>Selection bias: random sequence generation</th>
<th>Selection bias: allocation concealment</th>
<th>Detection bias: blinding of outcome assessment Hba1c</th>
<th>Reporting bias: selective reporting</th>
<th>Other bias</th>
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<td>Price (2016)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: PEO: psycho-educational outcomes, + indicates high risk of bias, - indicates low risk of bias, and ? indicates unclear risk of bias

^a cross-over design inappropriate  
^b baseline imbalance  
^c high risk for knowledge only  
^d insufficient information for reasons of drop-outs and methods of imputation for missing values
3.3.3 Effectiveness of interventions

3.3.3.1 Glycated haemoglobin (HbA1c)

Nine RCTs (67, 68, 79-81, 83-86) of 1,838 CYP with T1D evaluated the effectiveness of educational and psycho-educational interventions in reducing HbA1c and were included in the meta-analysis. As shown in Figure 7, effect sizes in four out of the nine trials showed a reduction in glycaemic control attributable to the intervention. The meta-analysis did not show a statistically significant glycaemic effect (pooled SMD= -0.06, 95% CI: -0.21 to 0.09). The intervention effect corresponded to a decrease in HbA1c of 0.1% (95% CI: -0.4% to 0.2%). There was moderate heterogeneity between the studies (I^2= 59.9%). An early trial of an educational intervention (68) with poor methodological quality fully explained this heterogeneity. Omission of this trial from the meta-analysis did not change the overall conclusion (SMD= -0.02, 95%CI: -0.13 to 0.09, I^2= 0%).

As shown by the subgroup analyses, the intervention effect on HbA1c remained non-significant for purely educational interventions (SMD= -0.17, 95% CI -0.88 to 0.55, three studies pooled), psycho-educational interventions (SMD=0.01, 95% CI: -0.01 to 0.02, six studies pooled), or interventions focusing only on adolescents (SMD=-0.05, 95% CI -0.20 to 0.10, four studies pooled).
Figure 7. Random effects meta-analysis of change scores in HbA$_1$c (%) in psycho-educational intervention group compared with control group.

Note: Intervention effects calculated as Standardised Mean Difference (SMD) with 95% confidence interval. A negative effect indicates better glycaemic control attributable to the intervention.

3.3.3.2 Psychosocial functioning

Interventions measured several indicators of psychosocial functioning. Results of the meta-analyses of intervention effects on psychosocial outcomes are shown in Figure 8. Four trials of one educational (85) and three psycho-educational interventions (67, 79, 83) assessed the effect of interventions on increasing self-efficacy. Overall,
interventions conferred a non-significant improvement in self-efficacy (SMD= 0.30, 95% CI: -0.16 to 0.76, $I^2$= 70.6%). When the one educational intervention (85) was removed, heterogeneity was reduced, and the effect of psycho-educational interventions on self-efficacy increased in magnitude and became statistically significant (SMD=0.50, 95% CI: 0.13 to 0.87, $I^2$= 27.8%). The meta-analysis provided no evidence for a beneficial effect of psycho-educational interventions on other aspects of psychosocial functioning, including diabetes-specific quality of life, general quality of life, psychological distress and family functioning. Additional psychosocial indicators were investigated in isolation, but no significant changes were found between the groups; these included patient empowerment (81), locus of control (79), health care climate (86), and patient enablement (86).
Figure 8. Intervention effects on psychosocial outcomes calculated as Standardised Mean Difference (SMD) of change scores with 95% confidence interval.

Note: A positive SMD in quality of life, self-efficacy, and family functioning and a negative effect is psychological distress are beneficial effects that favour the intervention. The diamonds show the pooled SMD based on random effects model. SED= Self-efficacy for diabetes; PedsQoL-D= Paediatric quality of life inventory: diabetes module; DQoLY= Diabetes Quality of life measure for youths (reverse scaling); PedsQoL-G= Paediatric quality of life inventory: generic scale; PAID =Problem Areas in Diabetes scale; SDQ= Strengths and Difficulties Questionnaire- impact score; ECBI= Eyberg child behavior inventory; PIP =Paediatric Inventory for parents; WBQ= Well-being questionnaire (reverse scaling); DFRQ= Diabetes Family Responsibility Questionnaire (dyadic score in Christie (2014) and parental report in Murphy (2012)); DFCS=Diabetes family conflict scale; DFBS= Diabetes Family Behavior scale
3.3.3.3 Diabetes knowledge

Five RCTs (one educational (68) and four psycho-educational (67, 79, 80, 83)) measured diabetes knowledge using comparable scales (87-89). Four trials (67, 68, 79, 83) could be pooled in the meta-analysis. With a random effects model, psycho-educational interventions had a non-significant effect on diabetes knowledge, in all cases measured immediately after the end of the intervention (SMD= -0.11, 95% CI: -0.45 to 0.23, I²= 40.5%). Between trial-heterogeneity was fully explained by an early trial of an educational intervention which was the only one to show a beneficial effect (68). One study provided insufficient data for the meta-analysis but reported no difference in post-intervention diabetes-related knowledge scores between the intervention and control group (80).

3.3.3.4 Adverse outcomes

Seven trials (67, 80, 81, 83-86) provided a report on the incidence of hospital admissions due to diabetic ketoacidosis (DKA) and hypoglycaemia, but none reported any increase of adverse outcomes related to the intervention. Insulin requirements were evaluated in six trials (67, 68, 80, 84-86) but data were unsuitable for a meta-analysis.

3.3.3.5 Other outcomes

The majority of included studies reported no change in insulin treatment (67, 68, 86) or in the percentage of children who moved to insulin pump therapy during the intervention (85). Only two RCTs targeting groups of families found a significant increase in the insulin dose (80) or in the frequency of insulin adjustment (84) in the intervention group. One trial examined whether intervention improved children’s adherence to diet (81) but found no change. Finally, four trials evaluated the effect of
interventions on the utilisation of health services (e.g. clinic visits (80, 83, 86), hospital admissions or contacts (68, 80, 86), and use of emergency hotline (83)) but none found any significant change.

3.3.4 Publication bias

Figure 9 shows the funnel plot of intervention effects in the primary outcome in the included trials. Visual examination of the funnel plot shows a slightly asymmetric scatter which is mainly due to the presence of a small outlying study with a negative effect.

Figure 9. Funnel plot of intervention effects in HbA1c in included studies
The current review identified ten UK-based randomised trials comparing psycho-educational interventions for improving management of T1D for children and young people with a control group of standard care or attention control. Interventions covered a range of approaches, from educational programs to interventions combining educational with psychological components. Pooled data from nine RCT showed that psycho-educational interventions conferred no glycaemic benefits over that achieved with standard care. Interventions with psychological components aiming to increase children’s self-efficacy showed a moderate beneficial effect. Nevertheless, no evidence was found of improvement in diabetes knowledge or other markers of psychosocial functioning, including quality of life, psychological distress, and family functioning.

As opposed to findings of the current review, two earlier meta-analyses primarily based on trials from North America (65, 66) found significant glycaemic benefits of psycho-educational interventions in children and adolescents corresponding to reductions in HbA1c by around half percentage point. They also provided support for significant psychological (65) and educational benefits (66). The important question is, therefore, why such a discrepancy between findings of the current review and that of previous reviews occurs. A number of explanations could be proposed.

First, earlier reviews were typically based on “efficacy” trials taking place in non-clinical settings and delivered by specialist practitioners with a background in psychology. By contrast, most of the UK interventions were “pragmatic” trials delivered by non-specialist interventionists, mostly nurses and dietitians, who had
received some training. In fact, only one UK intervention was delivered by a psychologist (79); this was a motivational interviewing intervention which found the greatest benefit in psychological outcomes, while also showing some indication for lower HbA1c. Two other interventions in the UK (80, 86) tried to incorporate components of motivational interviewing technique into everyday clinical practice by training non-psychologists but found no improvement in glycaemic and other outcomes.

Findings from interventions on adults with type 2 diabetes have shown that psychological and general health professionals are equally effective in delivering psychological interventions (90). However, available evidence for childhood T1D is limited. Some of the most successful psychological interventions in children with T1D have been delivered by interventionists with a background in psychology (91-95). This seems to suggest that the training and skills of the person delivering the intervention in children could have an impact on outcomes. As the number of psychologists in the UK diabetes services is small (96), “efficacy” interventions may not be easily applied to the NHS. However, it might be worthwhile to ensure that future interventions are delivered by rigorously trained personnel who have psychological training.

Earlier reviews also used different eligibility criteria and included trials in which the control group received care other than standard, i.e. intensive insulin treatment or less intensive psychological treatment. One of the interventions included in the current review (83) also involved a third arm receiving both the psycho-educational intervention and intensive insulin treatment and found a significant reduction in HbA1c by 1% as compared to standard care alone. Even though a different design would be needed to separate the intervention effect from the effect of intensive therapy, this
finding indicates that psycho-educational interventions could facilitate the uptake of intensive therapy schemes potentially enhancing their glycaemic benefits. Similar conclusions have been supported by US studies (94, 97) which showed that psychological interventions used in combination with intensive treatment conferred significant benefits in both glycaemic and psychosocial outcomes as compared to intensive treatment alone.

Although a lack of evidence for beneficial effects of UK psycho-educational interventions might reflect an absence of any “real” effect, there are other potential explanations. The “ceiling effect” is one possible explanation. Poor participation rates observed in most UK trials indicate that children entering trials might represent a population who already have reached a certain level of education and motivation in such a way that any additional intervention may not have a visible effect on their psychological or physical health. Even the observed benefit in children’s self-efficacy did not translate into glycaemic improvements typically measured one year after the end of the intervention. A longer duration with provision of extended support even after the end of the intervention together with a longer follow-up period might be needed for the behavioural modifications to influence the metabolic sequelae and translate into HbA1c reductions.

Lack of intervention “reach” is a potentially significant factor impacting on the effectiveness of such interventions. The above might highlight the need to develop new and innovative strategies to decrease patient burden and encourage patient commitment in future UK trials. Poor study enrolment and high withdrawal rates had also led to small sample sizes. In fact, only half of the UK trials had adequate power to detect an intervention effect. Since power calculations were predominantly based
on glycaemic control, small sample size was most problematic for evaluation of psycho-educational outcomes. In addition to that, attendance rates were unsatisfactory and, in some trials, attendance was insufficient to demonstrate any potential effect.

Most of the UK interventions were offered to adolescents who were diagnosed with T1D for more than one year. Those children might have already established management strategies and behavioural patterns that are difficult to challenge and ultimately change. This might also be a reason explaining adolescents’ hesitance to participate as they tend to view such interventions as “non-essential”. Although targeting younger and newly diagnosed children can be challenging given the complex adaptation processes taking place, evidence from US trials indicates that implementation of psycho-educational programs earlier in the course of diabetes has the potential to provide a more effective framework for such interventions (98, 99).

The systematic review also found that although all interventions were theoretically grounded, they were poorly described, particularly as far as the components of the intervention and the type of standard care are concerned, making it difficult to be replicated in practice. Educational and psychological interventions conducted in the UK also showed considerable heterogeneity in their content, intensity, selection of outcomes and delivery. Attrition and reporting bias, especially with regard to psychosocial outcomes, was an issue in some studies and further complicates interpretation of findings.

This is the first focused review to evaluate the effectiveness of psycho-educational interventions on CYP with T1D in the UK. A rigorous protocol was used with high sensitivity and specificity to detect included studies. Psychosocial outcomes were
grouped into conceptually similar constructs, which allowed the examination of intervention effects across distinct aspects of psychosocial functioning. However, there are limitations which need to be considered. Firstly, the review was restricted to UK trials, and therefore no direct comparisons between UK and non-UK interventions could be made. Second, the variability in the scales used to measure psychological outcomes and the differences in follow-up between different interventions resulted in considerable heterogeneity between studies and require exercising caution when interpreting the findings. Moreover, half of the included trials provided a single follow-up measurement which prevented any meaningful stratification of the analyses by follow-up interval. It was also impossible to assess the effect of interventions on long-term metabolic control since none of the included studies followed participants for more than two years. Third, the small number of eligible trials did not allow examination of possible modifiers, such as age, diabetes duration and type of intervention. Finally, the review included only published studies. Even though a comprehensive literature search was conducted and “snowballing” techniques were used to locate eligible studies, the potential of publication bias cannot be eliminated.

3.4.1 Conclusion

There is insufficient evidence to recommend the adoption of psycho-educational programmes for children and adolescents with T1D in the UK. The fact that similar interventions have been successfully implemented in the US and other countries indicates that such interventions are not inherently ineffective. Assessment of their impact on diabetes outcomes requires focusing attention on target populations and on the context within which they are implemented. One striking difference between UK and non-UK successful trials has been the involvement of psychologists in the delivery
of psychological interventions, which may be relevant to the deferring success. Future UK trials could benefit from the active participation of psychological specialists in the delivery of psychologically informed interventions and the provision of rigorous training of interventionists in psychological and clinical aspects related to diabetes. More attention could also be given to the earlier implementation of such interventions (e.g. in younger or newly diagnosed children) as well as to the provision of innovative approaches with the aim of encouraging the active participation and involvement of children, adolescents, and their parents.

3.5 Update of the systematic review

An update of the systematic review was conducted using the same search terms. Embase, Medline, and PsycINFO were searched between March 2016 and June 2018. One hundred and forty seven unique citations were identified, none of which met the eligibility criteria for the current review. One study evaluated the cost-effectiveness of an intervention that was already included in the current review (100).
Chapter 4  **Between clinic variation in glycaemic control for children with type 1 diabetes in England and Wales: what is the scope for improving outcomes by reducing clinic differences?**

4.1 **Background**

In the UK, there are at least 29,000 children under 19 years with T1D \((101, 102)\). Clinical management of children with diabetes in the UK is delivered by a multidisciplinary team in hospital-based paediatric diabetes units. Although several UK governmental and national organisations have set specific standards of care for children with diabetes \((58, 59, 96, 103)\), the glycaemic performance of England and Wales is quite poor. In 2012, less than one in five children and young people with diabetes in England and Wales met the NICE recommended Glycated Haemoglobin \(\text{HbA}_1c\) target of less than 58 mmol/mol \((7.5\%)\) \((104)\). In addition to that, results from the 2012 NHS Diabetes Atlas of Variation described wide regional variations in diabetes outcomes for children \((25)\), thereby highlighting the issue of unwarranted variation in paediatric diabetes care. Findings from the National Paediatric Diabetes Audit reports have supported these observations by consistently reporting substantial differences across paediatric diabetes clinics \((104)\). Narrowing of clinic variation was identified as a priority policy in the 2012 National Paediatric Diabetes Service Improvement Delivery Plan, which also set an aim to decrease national average levels of \(\text{HbA}_1c\) by 16 mmol/mol \((1.5\%)\) by 2023 \((105)\).

Findings of the systematic review reported in Chapter 2 showed that numerous studies have looked at variation in glycaemic control between paediatric clinics \((37, 38, 43, 47-51)\). However, most of them have examined clinic variation by only looking at
absolute differences between clinic means. This approach constitutes a major obstacle to effective policy action. In addition to looking at absolute differences between clinic means, it is essential to determine the share of the total variation in glycaemic control that exists between clinics (53, 54). This interpretation of clinic variation as a “relative” measure provides a better conceptualisation of the “bigger picture” and corresponds to the statistical concept of clustering (55). Understanding how health outcomes are geographically clustered across the population is of crucial importance for policy development and implementation (56). For example, if children’s glycaemic control is homogeneously achieved across clinics (i.e. showing low clustering), then policies aiming to reduce centre variation by targeting poorly performing clinics may narrowly miss most non-optimally controlled children in the country. Conversely, if glycaemic control is heterogeneously distributed across clinics (i.e. high clustering), then policies that target all clinics in the country will see available resources inefficiently delivered to areas at the smallest need.

Even though clustering of glycaemic outcomes across the entire population provides important information for policy making, differences between healthcare providers may be complex in such a way that they may not be the same for everyone. For example, while diabetes clinics may exert a more significant influence on glucose control of a particular group of children, they might not have the same impact on other populations. This is to be expected since children with different sociodemographic or disease characteristics display very different needs in relation to their interactions with the clinic environment. It is therefore important to identify for which population of children potentially unwarranted clinic variations are most prominent. This would allow tailoring policy actions to meet the needs of specific patient groups thereby increasing their potential for securing improvements.
4.1.1 Aims

The current chapter aims to determine the scope for improving children’s glycaemic outcomes by reducing variation between clinics. More specifically, the objectives are to (1) describe the extent of variation in glycaemic control between and within clinics; (2) explore the general contribution of clinics to understanding differences in children’s glycaemic outcomes, and finally to (3) examine whether choice of clinic matters more to specific populations of children based on their sociodemographic or disease profile and method of insulin delivery.

4.2 Methods

4.2.1 Study design

This study is a secondary analysis of data from the National Paediatric Diabetes Audit (NPDA). The study included all children aged <19 years with T1D who received care in all of the 177 paediatric diabetes clinics in England and Wales between April 1, 2012, and March 31, 2013 (104). Newly diagnosed children with a duration of diabetes of fewer than three months were excluded since levels of HbA1c close to diagnosis are not reflective of ongoing diabetes control. The following children were also excluded: 251 children who changed clinic during the audit year, and children with missing information on age (n=3), gender (n=9), ethnicity (n=121), deprivation (n=190) and duration of diabetes (n=208). To ensure processed data can not be attributed to identifiable individual children (e.g. a child with diabetes in a small clinic from a sparsely populated area might be linked with other freely available information, such as social media, to identify an individual), small clinics treating less than ten children
were excluded from the analysis. One clinic with one eligible child was excluded leaving a final population of 21,773 children across 176 clinics.

4.2.2 Measures

4.2.2.1 Outcome variable

Glycaemic control was the outcome of interest and was assessed by levels of HbA1c. HbA1c was reported in standardised concentrations of mmol/mol in accordance with the International Federation of Clinical Chemistry (IFCC) (106). HbA1c values submitted to NPDA in Diabetes and Complications Trial (DCCT) units of percentage were converted to mmol/mol using the formula: IFCC (mmol/mol) = (10.93 × DCCT (%)) -23.50 (107). The mean HbA1c value over the audit period for each patient was used in the analyses. HbA1c measurements are reported in IFCC units (mmol/mol) together with DCCT units (%) in brackets.

4.2.2.2 Case-mix characteristics

A set of potentially confounding case-mix variables was identified from the literature in order to adjust for glycaemic determinants which are beyond the control of the clinic without removing differences that may be attributable to the quality of diabetes care (108). The following five case-mix variables were considered: age (in years), gender, duration of diabetes (grouped in four categories: <12 months, 12-23 months, 24-59 months, and >60 months), small-area deprivation (5 quintiles) and self-reported ethnicity (coded as White, Mixed, Black, Asian, other and “not reported”). Interaction terms between age and duration of diabetes contributed significantly to the explanatory power of the model and were retained in the analyses. The residential post-code of each individual was assigned a deprivation score based on the 2010 and the 2011
Indices of Multiple Deprivation (IMD) for England (109) and Wales (110) respectively. The IMD combines several indicators in domains related to socioeconomic status, health, crime, and housing issues into a single score which is a relative ranking of small areas. An adjusted UK-wide IMD score was generated following established methodology (111).

4.2.3 Statistical analysis

Individual HbA1c was analysed by using random-intercept multilevel linear regression models with children at the first level and clinics at the second level. In this way, the total variation in HbA1c was deconstructed into two components: variation between clinics and variation within clinics (i.e. between children) (55). A schematic representation of this decomposition of the total variation in HbA1c is shown in Figure 10 below.

Figure 10. Schematic representation of the decomposition of total variation in HbA1c into variation between clinics and variation within clinics. Black dots around clinic mean HbA1c values (thick black horizontal lines) represent individual HbA1c values.
To understand what scope for national improvements in glycaemic outcomes would be possible by reducing between-clinic variation, we need to consider variation between clinics relative to the total variation (53, 54, 112). For this reason, the Intraclass Correlation Coefficient (ICC) was calculated. ICC is the proportion of total variation in glycaemic control which occurs between clinics, i.e. 

\[ ICC = \frac{\text{between clinic variance}}{\text{between clinic} + \text{within clinic variance}} \] (113). Large values of ICC provide evidence of large variations in performance across clinics. This is interpreted as being indicative of marked differences in glycaemic performance that may be amenable to clinic-based interventions.

To visualise variation between adjusted clinic means, clinic estimates (i.e. residuals) derived from the adjusted two-level model were plotted with 95% CI. The above clinic estimates are similar to comparing clinics as if they had the same composition of children regarding case-mix characteristics. Clinic estimates from multilevel models include a “shrinkage factor” according to which less precise estimates from smaller clinics are weighted towards the national average. This is important to correct for random variation (i.e. due to chance). The case-mix adjusted model identified three classifications for clinics; clinics whose CI limits crossed the national average were classified as “average”. Clinics for which the upper 95% CI limit was lower than the national average were considered as performing “better than average”, while clinics whose lower 95% CI limit was above the national average were considered as performing “poorer than average”. To further illustrate the potential implications of adopting a clinic-based approach to improve glycaemic control at a national level, the proportion of children with good (<58 mmol/mol; 7.5%), moderate (58-80 mmol/mol; 7.5%-9.5%) and poor glycaemic control (>80 mmol/mol; 9.5%) in each of the three
clinic classifications identified by the two-level case-mix adjusted model were calculated.

The previous case-mix adjusted (random-intercept) two-level model provided a single ICC for the whole T1D population. However, the context of clinic might be stronger for specific groups of children while it may be less influential for others. To explore this aspect, the previous case-mix adjusted two-level model was extended by running a series of complex variance models in which both components of variance (i.e. within clinic and between clinics) were modelled as a function of individual variables including case-mix variables and use of insulin pump. This allowed calculation of the Variance Partitioning Coefficient (VPC) (114). VPC is the percentage of total variance in HbA1c attributable to differences between clinics. VPC is similar to ICC with the only difference that the proportion is no longer constant but is allowed to take different values for diverse types of patients. Individual variables were introduced one at a time in the random part of both within and between clinic variance functions. Different functional forms of random parameters were specified at each level (i.e. constant, linear, or quadratic) and the likelihood ratio test was used to retain the form which fitted the national data best. To ease interpretation and assist model convergence, diabetes duration (<2 vs ≥2 years) and ethnicity (white vs non-white) were entered in the variance functions as binary variables. Deprivation quintiles were introduced as continuous variables. Age was treated both as a continuous and categorical variable (0-4, 5-9, 10-14 and 15-18 years).

Data for insulin regimen were missing for 2,933 children (13.5%) with 19 clinics contributing to 90% of missing values. To minimise loss of information, missing data on insulin regimen were imputed using Multiple Imputation Chained Equations under
a missing at random assumption (115). Imputation models included all model variables (including outcome and interaction terms) plus a number of auxiliary variables (BMI, cholesterol, systolic and diastolic blood pressure). Clinic mean HbA1c values were used to accommodate the pattern of missing data and take account of clustering in the imputation model (116). Multilevel analyses were run across 20 imputed datasets, and parameters from each dataset were combined to obtain overall estimates using Rubin’s rules (117). Analysis of imputed insulin regimen data provided equivalent results to complete case analysis.

All statistical analyses were performed using Stata v.13 and MLwiN v2.33. Parameters of multilevel models were estimated by the maximum likelihood method, and goodness of fit was assessed by -2 log likelihood with smaller values indicating a better fit. All categorical variables were included in the model as dummy variables taking values of either 1 (representing membership to a category) or 0 (representing non-membership). Comparison between subsequently fitted nested models was made using the deviance (Likelihood Ratio) chi-squared test at the significance level of 0.05. Random-effect parameters are presented as variance estimates together with their standard error. For the complex variance models, an unstructured covariance matrix was used to allow for flexibility in the correlation between intercepts and slopes. In the current thesis, the terms variance and variation are used interchangeably.

4.3 Results

4.3.1 The extent of variation in glycaemic control between and within clinics

The characteristics of children and clinics are presented in Table 8. The sample consisted of 21,773 children with T1D (52.6% male) receiving care from 176 clinics.
Children were predominantly white (79.5%), had an average age of 12.3 years (SD=3.8) and 41% had diabetes for more than five years. Mean HbA1c was 72.4 mmol/mol (SD=17.4). The middle 50% of clinics (i.e. interquartile range) had a mean HbA1c ranging from 69.5 to 75.6 mmol/mol. Clinics varied considerably in their ethnicity (IQR for % of white children: 68.1%-97.8%) and deprivation make-up (IQR for % of children in the most deprived quintile: 8.3%-29.6%).
Table 8. Case-mix characteristics of children and diabetes clinics included in the study.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No of children (%)</th>
<th>Median %&lt;sup&gt;a&lt;/sup&gt; (middle 50% range- IQR) across clinics</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>1,203 (5.5)</td>
<td>5.4 (4.0 to 6.8)</td>
</tr>
<tr>
<td>5-11</td>
<td>7,656 (35.2)</td>
<td>35.3 (30.2 to 40.0)</td>
</tr>
<tr>
<td>12-18</td>
<td>12,914 (59.3)</td>
<td>59.9 (54.3 to 64.5)</td>
</tr>
</tbody>
</table>

Gender:
- Male: 11,444 (52.6) 52.2 (49.4 to 55.6)
- Female: 10,329 (47.4) 47.8 (44.4 to 50.6)

Diabetes duration (years):
- < 1: 3,606 (16.6) 16.4 (13.8 to 19.6)
- 1: 2,618 (12.0) 12.0 (10.3 to 14.0)
- 2 - 4: 6,628 (30.4) 30.0 (27.5 to 33.5)
- ≥5: 8,921 (41.0) 41.4 (37.4 to 44.9)

Index of multiple deprivation quintiles:
- 1 (least deprived): 4,359 (20.0) 16.1 (7.1 to 26.3)
- 2: 4,354 (20.0) 19.4 (13.8 to 26.3)
- 3: 4,354 (20.0) 19.4 (14.6 to 24.6)
- 4: 4,352 (20.0) 20.1 (13.7 to 26.4)
- 5 (most deprived): 4,354 (20.0) 15.1 (8.3 to 29.6)

Ethnicity:
- White: 17,317 (79.5) 90.5 (68.1 to 97.8)
- Asian: 1,083 (5.0) 1.1 (0 to 6.0)
- Mixed: 575 (2.6) 1.4 (0 to 3.2)
- Black: 409 (1.9) 0 (0 to 1.1)
- Other: 305 (1.4) 0 (0 to 1.3)
- Not reported: 2,084 (9.6) 0 (0 to 6.5)

Insulin regimen:
- ≤ 3 daily injections: 2,825 (13.0) 5.6 (1.2 to 17.6)
- ≥ 4 daily injections: 12,761 (58.6) 66.8 (49.6 to 79.8)
- Insulin pump therapy: 3,254 (15.0) 12.8 (13.7 to 24.8)
- Missing: 2,933 (13.5) 0 (0 to 2.5)
- Total: 21,773 -

<sup>a</sup>Percentages of children in each group were calculated for each clinic. Percentages may not add up to 100 because of rounding.

IQR= interquartile range
Figure 11 illustrates how crude HbA_{1c} levels vary both within and between the 176 paediatric diabetes clinics in England and Wales as a “caterpillar plot”. The width of the box-and-whisker plots shows the spread of individual HbA_{1c} values within each clinic (i.e. within-clinic variation). Clinic means are represented by the diamond and their spread around the national average HbA_{1c} value of 72 mmol/mol (8.8%) (red horizontal line) reflects the degree of variability that exists between clinics (between-clinic variation). Two themes of note emerge from this figure. First, glycaemic control varies more within than between clinics as shown by the extensive overlap between the clinic individual distributions. Moreover, clinics with poorer mean glycaemic performance tend to have children with more variable glycaemic outcomes (i.e. higher within clinic variability).

Figure 12 shows the estimates of clinic means with 95% confidence intervals derived from the two-level, case-mix adjusted model. On average, adjusted clinic means deviated around the national average by 3.5 mmol/mol (HbA_{1c} of 0.3%). Clinics in the bottom 2.5% of the distribution had a glycaemic difference of around 14 mmol/mol (HbA_{1c} of 1.3%) as compared to clinics located at the top 2.5%. Overall, 69 of the 176 clinics (39%) had an adjusted HbA_{1c} value that deviated significantly from the national average (red horizontal line). Of them, 34 clinics performed significantly below the national average, and 35 performed significantly above the national average.
Figure 11. Box and whisker plots showing variation in HbA$_{1c}$ within each of the 176 diabetes clinics in England and Wales.

Note: The shaded box represents the interquartile range (IQR) capturing the middle 50% of children in each clinic. Whiskers extend to include all HbA$_{1c}$ values within 1.5 times the IQR beyond the upper and lower quartile for each clinic. Clinics are ranked according to their crude mean HbA$_{1c}$ (diamonds). The red horizontal line shows the national average of 72 mmol/mol (8.8%). The dashed line represents the NICE HbA$_{1c}$ recommended target at the time of the study. Individual outlying HbA$_{1c}$ values are not shown.
Figure 12. Estimates of clinic means with 95% confidence intervals after adjustment for differences in case-mix characteristics of children regarding age, gender, diabetes duration, ethnicity, and small-area deprivation.

Note: national average shown by the red horizontal line. The dashed line represents the NICE HbA1c recommended target at the time of the study. Intraclass Correlation Coefficient (ICC) = 4.7%. ICC represents the proportion of total variation in HbA1c which occurs between clinics.
4.3.2 General contribution of clinics to total variation in glycaemic control

To explore the contribution of clinics in explaining variation in children’s glycaemic outcomes, the proportion of the total variation that is located between clinics (i.e. ICC) was calculated and results are shown in Table 9 below. The unadjusted model showed that only 5.4% of the total variation occurred between clinics. After controlling for individual case-mix characteristics, ICC slightly reduced to 4.7%, with the remaining variation (95.3%) being located within clinics.

Table 9. Proportion of variance in children's glycaemic control attributable to differences between clinics

<table>
<thead>
<tr>
<th>Components of variance in HbA1c</th>
<th>Unadjusted model a</th>
<th>Case-mix adjusted model b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variance (SE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between clinics</td>
<td>16.4 (2.1)</td>
<td>12.4 (1.6)</td>
</tr>
<tr>
<td>Within clinics</td>
<td>287.6 (2.9)</td>
<td>249.5 (2.4)</td>
</tr>
<tr>
<td>% of total variance attributable to differences between clinics - ICC</td>
<td>5.4%</td>
<td>4.7%</td>
</tr>
<tr>
<td>-2Log likelihood</td>
<td>185,408</td>
<td>182,295</td>
</tr>
</tbody>
</table>

Two-level models with a random effect for clinic. SE=standard error, ICC=Intraclass Correlation Coefficient.

a No explanatory variables

b Adjusted for age, gender, diabetes duration, age-duration interaction, ethnicity, and deprivation

Table 10 shows how children with different levels of glycaemic control are distributed across clinics with different glycaemic performance as compared to the national average (better than average, average, poorer than average). Of the 5,333 children with a poor glycaemic control, 1,546 (28%) received their care in one of the 35 clinics performing poorer than average. Although this is higher than the 19% (i.e. 35 clinics...
out of 176) expected by chance, most poorly controlled children (3,997 out of 5,533 or 72%) were treated by non-poorly performing clinics.

Table 10. Number of children (%) with different levels of glycaemic control by clinic classification based on adjusted glycaemic performance

<table>
<thead>
<tr>
<th>Individual HbA1c – mmol/mol (%)</th>
<th>Clinic classification of glycaemic performance</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Better than average (n=34)</td>
<td>Average (n=107)</td>
</tr>
<tr>
<td>&lt;58 mmol/mol (7.5%)</td>
<td>1,389 (36%)</td>
<td>2,022 (52%)</td>
</tr>
<tr>
<td>58-80 mmol/mol (7.5%- 9.5%)</td>
<td>3,178 (26%)</td>
<td>7,122 (58%)</td>
</tr>
<tr>
<td>&gt;80 mmol/mol (9.5%)</td>
<td>848 (15%)</td>
<td>3,139 (57%)</td>
</tr>
</tbody>
</table>

Note: percentages refer to the total number of children in each glycaemic category and may not add up to 100 due to rounding. Classification of clinics into categories is based on the 95% confidence intervals of the clinic estimates obtained from the case-mix adjusted model with a random effect for clinics. Adjustment was made for individual gender, age, duration of diabetes, ethnicity, and small-area deprivation.

#### 4.3.3 Importance of clinic effect for specific groups of children

Figure 13 shows results obtained from the complex variance models in which both components of variance (i.e. within clinic and between clinics) were modelled as a function of individual variables. As compared to the total population of children with T1D, the proportion of total variation in HbA1c that occurs at the level of the clinic (VPC) was higher in younger children aged < 10 years (10-13%) and in children receiving pump therapy (9%). Detailed results of the complex variance multilevel models are shown in Appendix B.
Figure 14 shows, in more detail, how differences (i.e. variation) in levels of HbA1c are partitioned between and within clinics with increasing age (age as a continuous variable). Two things are worth noticing. First, after the preschool period variation within clinics increases markedly with age. For example, within a given clinic, a 15-year-old adolescent is expected to have almost four times more variable HbA1c levels than a 5-year old child. Second, the increasing within-clinic variation attenuates the importance of clinic-level factors driving variation in glycaemic control, ultimately resulting in low levels of VPC in older children.
Figure 13. Proportion of total variance at the level of the clinic for different groups of children with type 1 diabetes.

Note: results derived from complex variance case-mix adjusted models in which both components of variance (i.e. within clinic and between clinics) are modelled as a function of individual variables (one at a time).

* Data for insulin regimen were missing for 2,933 children (13.5%) and were imputed using multiple imputation.
Figure 14. Components of variance in HbA1c and Variance Partitioning Coefficient (VPC) as a function of children’s age.
4.4 Discussion

The current study aimed to explore the importance of clinic context in the understanding of glycaemic differences in children with T1D. First, the magnitude of potentially unwarranted variation between diabetes clinics’ glycaemic control was examined by looking at differences between clinics after adjusting for differences in the case-mix composition of clinics with regard to important patient characteristics. This analysis showed that two out of five clinics in England and Wales had a glycaemic performance which differed significantly from the national average. More specifically, clinics with typically good glycaemic performance were found to have an HbA1c of 14 mmol/mol better compared to clinics with a typically poor glycaemic performance. On average, clinics deviated around the national mean of 72 mmol/mol by 3.5 mmol/mol. Since the HbA1c target for good control is <58 mmol/mol, the average deviation of 3.5 mmol/mol represents 25% of the reduction towards getting the national average down to optimal levels. The above figures illustrate that there is an appreciable amount of potentially unwarranted variation which needs to be addressed if optimal care is to be provided to all children with T1D regardless of the clinic they attend.

Practice variation was additionally expressed as a fraction of the total variability in glycaemic outcomes. This provided a better understanding of the scope for glycaemic improvements that might be possible by narrowing variation between clinics. This analysis showed that diabetes clinics explained only a small portion of the total variation in glycaemic control (i.e. 4.7%). Most of the variation in glycaemic control
occurred within clinics (rather than between clinics) and was potentially attributable to unmeasured characteristics related to the children rather than the clinic.

From a health policy viewpoint, concentrating on absolute differences between clinic mean values provides insufficient information. Rather, it is key to consider clinic differences as a share of the total variability in HbA1c (53, 54, 112). For example, it is possible to observe quite large differences between clinics and still have a low ICC if the variation that occurs within clinics is sufficiently large. This is exactly the situation revealed in the current study. As shown, interventions targeting only poorly performing clinics would fail to capture most children in need just because children with poor glycaemic control are quite evenly distributed across all clinics.

Although reduction of unwarranted practice variations should always be a key goal of all healthcare systems, findings of the current analysis suggest that nationwide improvements in glycaemic control might best be achieved not only by targeting poor services but also by focusing on children with poor glycaemic control all over the country regardless of the clinic they attend. That is, shifting the whole distribution of clinics to higher levels of quality. The recent change in NICE guidelines for children with T1D towards tighter HbA1c control of less than 48 mmol/mol (6.5%) in 2015 (19) could help towards this direction. Patient-centred policies have also been shown to facilitate whole system improvements (118). For example, the recent introduction of patient reported experience measures (PREM) in England and Wales (119) can be used as a useful tool to encourage local changes in all clinics, even those identified as performing well.
After determining the general impact of clinic context on children’s glycaemic control, an additional analysis was conducted to explore whether the clinic environment mattered more for the glycaemic outcomes of particular groups of children. Results of this focused analysis suggested that the clinic context had a greater impact on younger children and on children who received pump therapy, with the proportion of variation in HbA1c attributable to clinic differences in those two groups of children being twice as high as that in the general population. Knowledge of this differential impact can provide a more explicit route for policy action by planning interventions tailored to the specific needs of these groups of children.

Children 0-9 years represent a small fraction of the total population of children with T1D (i.e. 27% in our study). However, their number is predicted to rise, given the well-recognised trend towards earlier onset of T1D (10). The high VPC in the youngest age-groups suggests that clinics could exert a greater influence on their glycaemic control. This seems to indicate that clinic-level interventions targeting younger children might be of some merit. Such clinic-based interventions could focus on parental education and level of involvement as younger children depend primarily on their caregivers for their glycaemic control.

For older children, clinics seemed to play a less relevant part for their glycaemic control. In the 15-18-year age group, less than 3% of the differences in children’s glycaemic control was attributable to the clinic. This is unsurprising. Adolescents represent a difficult-to-reach group with established behaviours and management strategies that are difficult to challenge and change. Children aged 10 years or above form the largest population of children with T1D but have a distinctive glycaemic profile. We showed that not only do they have, on average, poorer glycaemic control,
but they also tend to be more variable in their HbA1c levels. Putting it differently, within a given clinic, a healthcare professional is likely to see more adolescents at the extremes of the glycaemic spectrum. From a health policy perspective, targeting older children would require a “whole system” approach encouraging changes even in the best clinics in the country. Operation of highly-resourced, adolescent clinics within existing units is an example of such an approach. Specialist clinics could provide age-appropriate health and lifestyle education, also allowing a smoother transition to adult care.

The higher VPC in insulin pump users (i.e. VPC of 9%) compared to pen users (VPC of 4%) might reflect differences in therapeutic practices between diabetes clinics, such as different criteria for initiation of pump therapy and different training programs for pump use. Glycaemic control of pen users seems to be less influenced by the clinic where they receive their care. It is likely that factors affecting glycaemic management in pen users are less susceptible to clinic-level characteristics.

The current study has particular strengths. A multilevel analytical approach provided a robust framework for analysing hierarchical data. The large number of clinics and the use of nationally representative data provided high power to test for random effects and increased the external validity of the findings. There are also apparent limitations. First, this was a cross-sectional analysis which precludes us from making any causal inferences. Although an effort was made to adjust for important glycaemic determinants which are exogenous to the clinic environment, case-mix adjustment was limited by the fact that not all patient characteristics were measured. Unmeasured glycaemic determinants such as parental education, family environment, health-risk behaviours, and physical activity could systematically vary from one clinic to another.
and therefore explain further some of the clinic variability. Other than variations in performance, “clinic effects” may also be picking up factors such as variations in data collection or data entry, differences in laboratory methods, or differences in the actions of other geographically defined agencies, such as local government. For example, children attending the same clinic might also come from the same neighbourhood in which case “clinic effects” might partly echo underlying “small-area effects”. To explore this, cross-classified models were constructed, but the proportion of variance at the level of the clinic remained unaffected.

4.4.1 Conclusion

A multilevel analysis of national audit data on children with T1D in England and Wales revealed that glycaemic control is influenced by the clinic a child attends over and above individual characteristics. Clinic differences accounted for only a small portion of the total variation in glycaemic control with most of the variation being located within clinics. This indicates that quality improvement at a national level might best be achieved not only by targeting poor clinics in order to narrow centre variation, but also by “shifting the curve” of overall paediatric diabetes practice towards higher quality. However, the magnitude of clinic effect was not the same for all populations of children with T1D. Clinics exerted a greater influence on the glycaemic control of younger children and on children who received insulin via pumps. This suggests that focused, clinic-level interventions targeting the needs of younger children and children on insulin pump therapy might be of some merit.
Chapter 5  Can service-related factors explain the influence of clinic context on children's glycaemic control? The role of insulin regimen, regional networks, clinic volume, and within-clinic variability.

5.1  Introduction

Analysis of the components of variation in HbA1c so far has shown that most of the variation in glycaemic control of children with T1D in England and Wales exists within clinics rather than between clinics. In fact, variance analysis revealed that only 5% of the variation in HbA1c was attributable to differences between clinics. Having quantified the magnitude of the relative “clinic effect” by establishing the share of total variation in HbA1c that occurs between clinics, the next step was to investigate whether service-related factors could explain the “effect” of clinic context on glycaemic outcomes.

5.1.1  Aims

The aim of the current chapter is to (1) determine whether the influence of clinic context can be explained by differences in insulin regimen or characteristics of the clinics (including organisation into regional networks, clinic volume, and within-clinic variability in glycaemic control), and (2) investigate whether the above characteristics of the clinics are associated with children’s glycaemic levels.
5.2 Methods

5.2.1 Study design

Data for the current analysis were derived from the 2012/13 National Paediatric Diabetes Audit. The analysis was conducted on a population of 21,773 children aged <19 years with T1D for more than 3 months who received care in one of the 176 paediatric diabetes clinics in England and Wales between April 1, 2012, and March 31, 2013. Details on selection of study population are given in the previous chapter.

5.2.2 Measures

5.2.2.1 Glycaemic control

Glycaemic control was the outcome of interest and was evaluated by plasma levels of HbA\textsubscript{1c} reported in standardised concentrations of mmol/mol. The mean HbA\textsubscript{1c} value over the audit period for each patient was used in the current analyses.

5.2.2.2 Service-related factors

Four factors related to diabetes care were considered: one measured at the individual level (insulin regimen) and three at the level of the clinic (regional network, clinic volume, and within-clinic glycaemic variability). Insulin regimen was classified as ≤3 injections/day, ≥4 injections/day and pump therapy. Three clinic-level variables were computed; these included the regional network to which the clinic belongs (10 regional networks in England and Wales), the total number of eligible children being served by the clinic (hereafter referred to as clinic size) and the standard deviation of individual HbA\textsubscript{1c} measurements within each clinic (within-clinic HbA\textsubscript{1c} variability).
Data for insulin regimen were missing for 2,933 children (13.5%). To minimise loss of information, missing data on insulin regimen were imputed using Multiple Imputation Chained Equations under a missing at random assumption as explained in Chapter 4. Imputation models included all individual and clinic-level model variables (including the outcome and interaction terms) as well as auxiliary variables (BMI, cholesterol, systolic and diastolic blood pressure). Clinic mean HbA1c was also included in the imputation model to take account of clustering in the imputation model (116). Multilevel analyses were run across 20 imputed datasets, and parameters from each dataset were combined to obtain overall estimates using Rubin’s rules. Imputed results were similar to those using observed values; imputed findings are presented only in the analysis examining the role of insulin regimen.

5.2.3 Statistical analysis

Individual HbA1c was analysed by using random-intercept two-level linear regression models with children at the first level and clinics at the second level. To ensure a fair comparison between clinics multilevel models were adjusted for case-mix composition of clinics with regard to individual age, diabetes duration, gender, ethnicity, and small-area deprivation (details on case-mix methodology have been described in the previous chapter). The two-level case-mix adjusted model was extended by separately introducing the four service-related factors (insulin regimen, regional network structure, clinic volume and clinic HbA1c-SD) and looking at changes in Intraclass Correlation Coefficient (ICC). ICC is the proportion of total variation in glycaemic control which occurs between clinics, i.e. $ICC = \frac{\text{between clinic variance}}{\text{between clinic + within clinic variance}}$ (113). Attenuation of the relative clinic effect was judged by reduction in ICC.
Following this, the association between the above factors and children’s glycaemic outcomes was explored. Clinic volume and HbA$_{1c}$-SD were simultaneously entered into the model to allow for the interdependence between clinic volume and within clinic variability. Although diabetes networks constitute a conceptually third hierarchical level (i.e. children nested within clinics nested within networks), they were included as a fixed effect in the model because their small number (i.e. 11) did not provide enough power to position them as a third hierarchical level (120). The inclusion of quadratic terms for clinic volume and HbA$_{1c}$-SD did not improve model fit indicating that their association with glycaemic control was adequately described as linear.

5.3 Results

The sample consisted of 21,773 children with T1D across 176 diabetes clinics. The characteristics of children and clinics are presented in Table 8 of the previous chapter. Clinic size ranged from 34 to 398 with a median of 105 children. The standard deviation of individual HbA$_{1c}$ values ranged across clinics from 11 mmol/mol (1.0%) to 25 mmol/mol (2.3%).

As shown in Table 11, ICC was only marginally affected when insulin regimen and clinic volume were fitted in the case-mix adjusted model (ICC slightly reduced to 4.5%). The inclusion of network structure in the model led to a moderate reduction in ICC to 4.2%. However, the addition of networks did not give a better fit to the national data compared to the case-mix adjusted model (p-value of LRT=0.06). In contrast, the addition of HbA$_{1c}$-SD explained almost half of the clinic variability leading to a substantial reduction in ICC to 2.4%. Figure 15 presents a different visualisation of the
variances estimates in Table 11 by showing the amount of unexplained variation in HbA1c in each of the above models starting from the crude model (presented in Chapter 4). As shown, 85% of the total variability in children’s glycaemic control remained unexplained even after adjusting for case-mix and treatment characteristics. Detailed results of multilevel models are presented in Appendix C.

The next objective was to explore the association of HbA1c with clinic characteristics after controlling for children’s case-mix profile. Figure 16 shows the predicted mean HbA1c values for each of the 11 regional networks after adjustment for case-mix and clinic effects. Although some statistically significant differences between individual networks are observed (e.g. East Midlands and South Central vs East of England), overall, there is considerable overlap in their confidence intervals.

Figure 17 shows how clinic volume and clinic HbA1c-SD related to children’s glycaemic control. Children who attended larger clinics and clinics with lower HbA1c-SD (i.e. more consistent glycaemic performance) had, on average, better glycaemic control. However, as shown by the difference in the slopes of the two lines, the magnitude of the association was larger for clinic HbA1c-SD (lower HbA1c by 9.8 mmol/mol, 95% CI 8.2 to 11.5 [0.9%, 95% CI 0.8 to 1.1] per 10 mmol/mol [0.9%] decrease in clinic HbA1c-SD) as opposed to clinic volume (lower HbA1c by 0.9 mmol/mol, 95% CI 0.2 to 1.5 [0.1%, 95% CI 0.02 to 0.14] per 100 children increase in clinic volume). Figure 18 and Figure 19 present the predicted average association of children’s HbA1c levels with clinic HbA1c-SD and clinic volume respectively together with the observed values.
Table 11. Proportion of variance in children’s glycaemic control attributable to differences between clinics

<table>
<thead>
<tr>
<th>Components of variance in HbA1c</th>
<th>Case-mix adjusted model&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Case-mix adjusted + insulin regimen&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Case-mix adjusted + clinic volume</th>
<th>Case-mix adjusted + networks&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Case-mix adjusted + clinic HbA1c-SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between clinics</td>
<td>12.4 (1.6)</td>
<td>11.8 (1.5)</td>
<td>11.9 (1.5)</td>
<td>11.0 (1.4)</td>
<td>6.0 (0.9)</td>
</tr>
<tr>
<td>Within clinics</td>
<td>249.5 (2.4)</td>
<td>246.6 (2.4)</td>
<td>249.5 (2.4)</td>
<td>249.5 (2.4)</td>
<td>249.5 (2.4)</td>
</tr>
<tr>
<td>% of total variance attributable to differences between clinics - ICC</td>
<td>4.7%</td>
<td>4.6%</td>
<td>4.5%</td>
<td>4.2%</td>
<td>2.4%</td>
</tr>
<tr>
<td>-2Log likelihood</td>
<td>182,295</td>
<td>-</td>
<td>182,290</td>
<td>182,277</td>
<td>182,195</td>
</tr>
<tr>
<td>p-value of Likelihood Ratio Test&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Ref.</td>
<td>-</td>
<td>0.02</td>
<td>0.06</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Two-level models with a random effect for clinic. SE=standard error, ICC= Intraclass Correlation Coefficient.

<sup>a</sup> Adjusted for age, gender, diabetes duration, age-duration interaction, ethnicity, and deprivation

<sup>b</sup> Data for insulin regimen were missing for 2,933 children (13.5%) and were imputed using multiple imputation

<sup>c</sup> 11 regional diabetes networks

<sup>d</sup> Tests whether adding individual and clinic variables to case-mix adjusted model significantly improves the fit of the model
Figure 15. Unexplained total variation in children’s glycaemic control partitioned between and within clinics in different models.
Figure 16. Predicted mean HbA$_1c$ levels for Paediatric Diabetes Networks

*Note:* data derived from linear regression model with a random effect for clinics adjusted for individual case-mix characteristics (age, gender, diabetes duration, ethnicity, and deprivation).
Figure 17. Association between within-clinic variability (HbA1c-SD), clinic volume and HbA1c levels.

Note: results derived from a two-level model with a random effect for clinic adjusted for children case-mix characteristics (age, gender, diabetes duration, ethnicity, and deprivation).
Figure 18. Association between within-clinic variability (HbA1c-SD) and HbA1c levels

Note: Blue line represents the predicted average association as derived from a two-level model with a random effect for clinic adjusted for children case-mix characteristics (age, gender, diabetes duration, ethnicity, and deprivation) and clinic size. Green dots represent the observed values.
Figure 19. Association between clinic size and HbA1c levels

Note: Blue line represents the predicted average association as derived from a two-level model with a random effect for clinic adjusted for children case-mix characteristics (age, gender, diabetes duration, ethnicity, and deprivation) and within-clinic variability (HbA1c-SD). Green dots represent the observed values.
5.4 Discussion

The current chapter aimed to gain a better insight into how the clinic context might impact on glycaemic outcomes. For this reason, the role of several factors related to diabetes care was examined. Firstly, insulin regimen was shown to have a small impact on ICC. This is consistent with other studies which also found that clinic differences could not be explained by either the type or dose of insulin treatment (47, 50, 51). The above finding indicates that aspects of diabetes care other than insulin regimen on offer might explain how clinics contribute to differences in children’s metabolic control.

A second factor that was explored was related to the organisation of diabetes clinics into regional networks. Regional networks were found to have a limited contribution to children’s glycaemic control after controlling for children and clinic differences. It is important to emphasise that the above finding does not indicate that regional networks have no important role to play in the way diabetes care is structured and delivered. Instead, diabetes networks could provide an efficient arena for the implementation of national guidelines and dissemination of interventions. Such a role can be implemented through a range of different activities including encouraging young people and carer participation, broadening of stakeholder engagement, mapping resources and staffing levels, and identifying areas of service improvement (121).

Another interesting finding was that children treated in larger clinics had better glycaemic control, regardless of their case-mix characteristics. This finding can be explained by the fact that small services provided in low population density areas may lack the necessary resources that allow for the multidisciplinary structure being feasible. The current findings are consistent with those obtained from a national survey.
in France which showed that clinics with more than 50 children had a lower crude mean HbA$_{1c}$ compared to smaller clinics (44). On the other hand, three other studies found no evidence for an association between clinic size and HbA$_{1c}$ (35, 36, 43). More interestingly, a multi-centre study from Germany and Austria showed that mean HbA$_{1c}$ among children treated in large centres (>100 patients) was higher by 0.2% as compared to small centres after controlling for patient mix and clustering (42). These divergent results might represent methodological differences in the way clinic size is treated (e.g. as a continuous or binary variable with different cut-offs).

The exact nature of the relationship between clinic volume and glycaemic outcomes is difficult to establish given the cross-sectional nature of the current study. For example, the volume-outcome relationship may result from doctors and other members of the diabetes team gaining more experience as they treat a higher number of children thus providing a better quality of care which, in turn, translates into improved glycaemic control (i.e. “practice makes perfect” hypothesis). An alternative explanation could be that clinics with a good reputation may attract more children (i.e. selective referral hypothesis leading to ‘reverse causality’). In any case, a reduction of 0.9 mmol/mol per additional 100 children is of little clinical significance when average values for most clinics in England and Wales are over 70 mmol/mol. Clinic size was also found to explain only a small proportion of the “clinic effect”. Taken together, these findings suggest that there are unlikely to be any meaningful effects from centralisation of paediatric diabetes units into higher volume centres.

Moreover, within-clinic variability was explicitly modelled as a clinic-level variable. It was found that, overall, children who attended clinics achieving consistent glycaemic results (i.e. low within clinic variability) had significantly better glycaemic
control. This finding is in line with results from the Hvidore study group who reported better glycaemic performance in centres where the multidisciplinary team set consistent glycaemic targets (30). Achieving consistent glycaemic performance requires focusing attention on the management of challenging populations of children and reflects a broad range of factors, including team cohesiveness, coordination of care, and goal setting. In addition to its association with glycaemic control, within-clinic variability was found to explain half of the “clinic effect”. Both findings indicate that achievement of consistent glycaemic results from a clinic could be used as a separate performance indicator in addition to average glycaemic levels.

As with the previous analyses, findings presented here should be interpreted in the light of potential limitations. The cross-sectional design of the study does not allow drawing any causal inferences between clinic characteristics and glycaemic outcomes. Also, case-mix adjustment was limited to measured variables. In fact, even after controlling for important individual-level case-mix variables and insulin treatment, only 15% of the total variation in the outcome was explained, most of which was located within clinics (i.e. between children) rather than between clinics. This means that 85% of the variation in the outcome was left unexplained and was potentially attributable to unmeasured individual characteristics. Finally, use of audit data means that errors due to data collection and data entry cannot be excluded.

5.4.1 Conclusion

In conclusion, analysis of national audit data in England and Wales showed that the type of insulin regimen could not adequately explain the impact of clinic environment on the glycaemic outcomes of children with T1D. Similarly, the volume of the clinic
and the regional network where the clinic belongs made a limited contribution to children’s glycaemic levels. Although children who attended larger clinics had better glycaemic control, the magnitude of the association was not clinically significant. On the other hand, achievement of consistent glycaemic performance explained half of the clinic variability and children who attended clinics with less variable glycaemic results had significantly better glycaemic control. This suggests that variation between patients within each clinic is an important clinic characteristic and consistently optimal results within each clinic should be aimed for.
A workforce survey of paediatric diabetes services: How staffing levels compare between the four UK nations and within England? Are more staff associated with improved glycaemic control of children with type 1 diabetes?

6.1 Introduction

There is an overall agreement that a well-resourced multidisciplinary team lies at the heart of an effective model of paediatric diabetes care. Clinical guidelines in the UK recommend that all children and young people (CYP) with diabetes be managed by a multidisciplinary team, consisting of a consultant Diabetologist, a specialist nurse, a dietitian, and a psychologist or other mental health professional (122). Findings from the landmark DCCT trial have demonstrated that intensification of diabetes treatment aiming for lower glycaemic control resulted in a significant reduction in the risk of diabetes complications (16). However, intensification of diabetes management included not only intensification of insulin treatment, but also a whole management package including frequent visits to the clinic, education and additional support from members of the multidisciplinary diabetes team.

Since 1988, five surveys of paediatric diabetes services have been conducted in the UK, with the most recent in 2008 revealing significant shortages in staffing levels (123). Nevertheless, the current state of the paediatric diabetes workforce in the UK is not known. The recent emphasis of diabetes management on patient empowerment, together with the shifting epidemiology of diabetes towards earlier diagnosis and the complexity of intensive insulin treatments add new challenges to paediatric diabetes services and their workforce. In the UK, the Royal College of Nursing has
recommended a ratio of fewer than 70 patients per paediatric diabetes nurse (124). However, there is a limited evidence base regarding the staffing levels and the skill mix needed to achieve optimal outcomes for children with T1D. So far, the role of staffing levels in childhood diabetes has been examined by only a few small-scale, regional UK studies (33, 36), none of which have found evidence for any association with children’s glycaemic control.

Given that a significant amount of the health budget is spent on the workforce, it is quite surprising that little attention has been given over the last years to research on aspects of the workforce and their role in diabetes outcomes. The current survey was also timely, given the recent introduction of Best Practice Tariff in England in 2012, which allows financial incentives for paediatric diabetes clinics that meet specific standards of care (125).

6.1.1 Aims

The current chapter focuses on the role of paediatric diabetes workforce, one of the most important inputs to paediatric diabetes care. More specifically, the objectives of the current chapter are to (1) assess how many health care professionals are involved in the care of CYP with diabetes in the UK, (2) explore how workforce features (including staffing levels, training, and experience) vary between services across the four UK nations and between the 10 regional diabetes networks within England, and (3) determine whether there is any association between workforce features and children’s glycaemic control.
6.2 Methods

6.2.1 Survey design

The survey was administered via an online questionnaire which was developed and piloted by a working group consisted of consultant paediatricians with experience in diabetes and endocrinology. Questionnaire items referred to the whole diabetes service (rather than to individual diabetes clinics) because some paediatric diabetes units operate more than one clinic in different geographical sites. The survey collected staffing information for all healthcare professionals involved in paediatric diabetes care. Additional information about the service included experience and training of consultants, provision of out-of-hours services, service volume, and achievement of Best Practice Tariff (in England only). Lead consultants from all identifiable paediatric diabetes services in England, Scotland, Northern Ireland, and Wales received survey links in their email addresses. Respective national diabetes network managers provided contact details of lead consultants. Two reminder emails were sent three and four weeks after the initial invitation. Survey data were collected over a two-month period from October to December 2014. The survey was supported by the British Society for Paediatric Endocrinology and Diabetes (BSPED), the Association of Children’s Diabetes Clinicians (ACDC), Diabetes UK and the National Paediatric Diabetes Networks.

6.2.2 Staffing levels

Staffing levels were defined as the number of whole time equivalents (WTE) staff contracted to work in paediatric diabetes care for each profession per service. In all analyses, staffing levels were adjusted for service volume by calculating the number
of WTE of a healthcare professional per 1,000 patients (staff-to-patient ratio). To allow comparisons with previous surveys and clinical guidelines, the number of patients per 1 WTE staff was also calculated (staff caseload).

6.2.3 Service-level analysis: how staffing levels compare between UK countries and within England regional networks

The first phase of the analysis aimed to describe the current state of paediatric diabetes workforce in the UK. A service-level analysis was conducted to compare workforce data between UK countries and within England regions. Since the purpose of this survey was to describe existing staffing levels in the UK, the service-level analysis included all CYP ≤ 24 years with diabetes cared for by the paediatric diabetes services (both type 1 and other types). The age cut-off was selected since the age of transition to adult diabetes care varies considerably across the UK paediatric diabetes units and can be extended up to the age of 24. Comparisons between countries and diabetes networks (within England) were tested with Kruskal-Wallis test for continuous outcomes and by a chi-square test for categorical outcomes. Descriptive survey data were aggregated at the UK, country, and regional network level and, unless otherwise stated, were presented as average values.

6.2.4 Individual-level analysis: are more staff related to better glycaemic control of children with type 1 diabetes in England and Wales?

In the second phase of the analysis, workforce data were linked to individual-level data from the 2014/15 National Paediatric Diabetes Audit with the aim of exploring potential links between staffing levels and glycemic outcomes for children with T1D. The linkage included all children aged <19 years with T1D for at least three months
who received care in paediatric diabetes services in England and Wales between April 2014 and March 2015 (3). Glycaemic control of children was assessed by plasma levels of HbA1c reported in standardised concentrations of mmol/mol. The average HbA1c value over the audit year for each child was used in the analysis. Children with missing information on case-mix characteristics (age, gender, diabetes duration, ethnicity, and small-area deprivation) were excluded (n=541). To avoid potential identification of individual cases, small clinics treating less than ten children were excluded from the analysis. One clinic with four children was excluded leaving a final study population of 21,070 children across 159 services.

A series of case-mix adjusted multilevel models with a random effect for service were run to examine the association between workforce variables and glycaemic control. All models were adjusted for case-mix characteristics of children including age (continuous variable), gender, duration of diabetes (continuous variable), ethnicity (6 categories: white, mixed, black, Asian, other, “not reported”), and small-area deprivation (5 quintiles). Workforce variables were entered one at a time into the models. Workforce variables included staff caseload (profession-specific and total), provision of psychological services, consultant specialisation (defined as at least one consultant having a CCT in diabetes and endocrinology), 24-hour access to advice from the team, and achievement of best practice tariff payments (in England only). There was no evidence for a non-linear association between staff caseload and glycaemic control as tested by addition of quadratic terms for staffing levels in the models. Finally, a number of cross-level interaction terms between service workforce variables and individual case-mix characteristics were tested to investigate whether the impact of workforce differs in children with different disease characteristics (i.e.
diabetes duration) or sociodemographic profile (i.e. age, gender, white vs non-white ethnicity, and deprivation quintile).

All analyses were performed using Stata v.12. A p-value of <0.05 was considered to be statistically significant.

6.3 Results

6.3.1 How staffing levels compare between UK countries and within England regional networks

Overall, 175 out of 188 diabetes services (i.e. 93% response rate) participated in the online survey, caring for a total of 29,711 CYP up to the age of 24 years diagnosed with diabetes. Table 12 presents the main survey findings across the four UK nations. Service volume differed significantly between countries (p<0.001), with median service size ranging from 89 patients in Wales to 228 patients in Scotland. Eighty-percent of the services provided out-of-hours support for diabetes management from members of the diabetes team (defined as 17.00-08.00 on weekdays and 09.00-09.00 weekends). However, only 43% of services provided 24-h access to advice from members of the diabetes team. In England, Best Practice Tariff (BPT) payments were achieved by 88% of services (118/134, 12 services with missing information). BPT achievement differed significantly across the networks (p=0.03) and ranged from 58% in London to 100% in North East, North West, and South Central regions. Eighty-eight per cent of the services receiving enhanced payments (i.e. 104/118) reported that they appointed new staff as a result of the enhanced payments.
6.3.1.1 *Total staffing levels*

Figure 20 presents the staffing levels for all members of the multidisciplinary diabetes team in each regional diabetes network in England and for each of the four UK countries. As shown, total staff-to-patient ratios were highest in England (24.4 WTE per 1,000 patients), followed by Scotland (21 WTE) and N. Ireland (17.2 WTE). Wales had the lowest staff-to-patient ratio with 15.5 WTE healthcare professionals per 1,000 patients. Separate results for each health care profession group are presented below.
Table 12. Summary of workforce survey findings by UK country.

<table>
<thead>
<tr>
<th></th>
<th>UK</th>
<th>England</th>
<th>Scotland</th>
<th>N. Ireland</th>
<th>Wales</th>
<th>p-value&lt;sup&gt;y&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participating services (response rate)</td>
<td>175 (93%)</td>
<td>146 (94%)</td>
<td>8 (73%)</td>
<td>7 (100%)</td>
<td>14 (100%)</td>
<td>-</td>
</tr>
<tr>
<td>Number of children and young people up to 24 years with diabetes</td>
<td>29,711</td>
<td>24,796</td>
<td>2,321</td>
<td>1,172</td>
<td>1,422</td>
<td>-</td>
</tr>
<tr>
<td>Service volume; median (range)</td>
<td>141 (35-625)</td>
<td>146 (35-460)</td>
<td>228 (135-625)</td>
<td>170 (80-257)</td>
<td>89 (40-210)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-h access to advice from members of the diabetes team&lt;sup&gt;a&lt;/sup&gt;</td>
<td>43%</td>
<td>49%</td>
<td>13%</td>
<td>29%</td>
<td>0%</td>
<td>0.002</td>
</tr>
<tr>
<td>Caseload per 1 WTE PDSN</td>
<td>73</td>
<td>71</td>
<td>76</td>
<td>110</td>
<td>88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PDSN: patient ratio &gt; 1:70</td>
<td>52%</td>
<td>58%</td>
<td>25%</td>
<td>14%</td>
<td>21%</td>
<td>0.003</td>
</tr>
<tr>
<td>Dietitians allowed to adjust insulin dose&lt;sup&gt;c&lt;/sup&gt;</td>
<td>50%</td>
<td>52%</td>
<td>75%</td>
<td>29%</td>
<td>29%</td>
<td>0.11</td>
</tr>
<tr>
<td>Consultant with a CCT in Endocrinology and Diabetes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>21%</td>
<td>24%</td>
<td>25%</td>
<td>0%</td>
<td>0%</td>
<td>0.07</td>
</tr>
<tr>
<td>Psychologist /MHP working in the service</td>
<td>82%</td>
<td>87%</td>
<td>88%</td>
<td>71%</td>
<td>29%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

WTE: whole time equivalent, PDSN: Paediatric Diabetes Specialist Nurse, CCT: Certificate of Completion of Training, MHP: Mental Health Professional.

<sup>a</sup> One service with missing information

<sup>b</sup> 11 services with missing information

<sup>c</sup> 10 services with missing information

<sup>y</sup> Service-level analyses comparing differences in outcomes between the four UK countries; Kruskal-Wallis test was used for continuous outcomes and chi-square test for categorical outcomes.
Figure 20. Whole Time Equivalent (WTE) of health care professionals per 1,000 children and young people ≤ 24 years with diabetes in the UK by Country/region.

Note: PDSN: Paediatric Diabetes Specialist Nurses, MHP: Mental Health Professionals.
6.3.1.2 Consultants and other doctors

Forty-two per cent of paediatric diabetes services were led by two consultants. Consultants’ average working experience (defined as years spent as a consultant) ranged from 8 years in N. Ireland to 13.9 years in Scotland. Only 17% of consultants (56/329, 17 consultants from 11 services with missing training status) had a Certificate of Completion of Training (CCT) in endocrinology and diabetes. However, the majority (93%) had received some form of training in paediatric diabetes. Twenty-eight per cent of services were also attended by at least one fully trained doctor other than a consultant. The ratio of consultants and other fully trained doctors per 1,000 CYP with diabetes differed significantly between the four nations (p<0.001) and ranged from 1.9 WTE in Wales to 3.5 WTE in Scotland and N. Ireland. England had an average ratio of 2.7 WTE with no significant differences between networks (p=0.05). Finally, twenty-nine per cent of the services (41/144, two services with missing data) were attended by trainee doctors.

6.3.1.3 Paediatric Diabetes Specialist Nurses (PDSN) and diabetes educators

All services were attended by at least one PDSN with 98% (483/493, 10 PDSN with missing data) of PDSN working in both hospital and community settings. In the UK, there was an average caseload of 73 patients for one WTE PDSN (or 13.8 WTE per 1,000 patients), with only 52% of the services meeting the Royal College of Nursing recommended nurse: patient ratio of >1:70. PDSN staffing levels differed significantly between the UK countries (p<0.001). Caseload per 1 WTE nurse ranged from 71 patients in England to 110 patients in N. Ireland. There were significant cross-network differences in PDSN staffing levels within England ranging from one nurse per 53
patients in North East to one nurse per 86 patients in East Midlands (p=0.01). Diabetes educators were defined as any member of the diabetes team outside the PDSN workforce responsible specifically for the structured education programme. Only 20 out of 175 services in the UK (11%) had a diabetes educator working as a member of the multidisciplinary team, with significant cross-country differences (0% in Wales vs 72% in N. Ireland, p<0.001).

6.3.1.4 Mental Health Professionals

Eighty-two per cent of diabetes services in the UK (143/175) had a mental health professional working as a member of the diabetes team. Most mental health professionals were clinical psychologists (87%), followed by health psychologists (3%), psychiatrists (2%), and other professionals. Staffing levels for mental health professionals showed significant differences between countries (p<0.001); In Wales, only 29% of services (4/14) were attended by a mental health professional with an average ratio of 0.1 WTE per 1,000 patients. England had the highest ratio of mental health professionals-to-patients (2.2 WTE per 1,000 patients) with staffing levels being quite evenly distributed across the regional networks.

6.3.1.5 Dietitians

All but one service (174/175) offered CYP regular dietetic support. Sixty-six per cent of dietitians (174/263, 12 dietitians with missing information) worked in both hospital and community settings, while 44% (113/256, 19 dietitians with missing data) could adjust insulin dose. Staffing levels of dietitians varied by 2.7-fold across the UK countries (p<0.001). The number of WTE dietitians per 1,000 patients was lowest in N. Ireland (1.8 WTE) and highest in England (4.9 WTE). Staffing levels of dietitians did not differ significantly between English regional networks (p=0.51).
6.3.2 Association between workforce characteristics and glycaemic control in children with type 1 diabetes

6.3.2.1 Staff caseload and glycaemic control

Table 13 presents the findings from the workforce-NPDA linkage analysis for the association between workforce variables and children’s glycaemic control in England and Wales after correcting for case-mix. On average, heavier total staff caseload by 50 children was associated with poorer glycaemic control by 1.5 mmol/mol. However, there was large uncertainty around this estimate (95% CI 0.01 to 3.0). The association between total staff caseload and HbA1c differ significantly according to children’s diabetes duration (p-value of total staff caseload-duration interaction term <0.001) and was stronger in children with a longer duration of the disease as opposed to newly diagnosed children. As shown in Figure 21, for example, an increase in total staff caseload by 50 patients was associated with a deterioration in HbA1c by 3.6 mmol/mol (95% CI 1.7 to 5.5) in children who had diabetes for 10 years. There was no significant association between profession-specific staffing levels and children’s glycaemic control. From the different staff categories, nursing caseload showed the strongest, though non-significant, positive association with glycaemic control (see Table 13). Nursing caseload showed a similar pattern of interaction with children’s duration status as that observed with total staff caseload (p-value of interaction term=0.004). No other significant interactions were found.

6.3.2.2 Association between other workforce aspects and glycaemic control

Children who attended a service with a psychologist had lower HbA1c levels by 1.7 mmol/mol (95% CI -3.2 to -0.2, p-value=0.03). The glycaemic difference was significantly higher among non-white children (lower HbA1c by 4.0 mmol/mol, 95%
CI -7.8 to -0.3; p-value of the interaction term between ethnicity and provision of psychological services=0.02). No other aspects of the workforce were found to be related to children’s glycaemic levels (see Table 13).
### Table 13. Associations between workforce and glycaemic control of children with type 1 diabetes in England and Wales

<table>
<thead>
<tr>
<th></th>
<th>Number of children (services)</th>
<th>Median (middle 50% range) across services</th>
<th>Change in HbA1c (mmol/mol) (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total staff caseload (per 50 increase)</td>
<td>20,735 (157)</td>
<td>35 (28 – 41)</td>
<td>1.5 (0.01 to 3.0)</td>
<td>0.048</td>
</tr>
<tr>
<td>Profession-specific caseload a (per 100 increase)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paediatric diabetes specialist nurse</td>
<td>21,070 (159)</td>
<td>83 (76 – 104)</td>
<td>1.2 (-0.04 to 2.5)</td>
<td>0.06</td>
</tr>
<tr>
<td>Consultant paediatrician</td>
<td>20,735 (157)</td>
<td>376 (238 – 476)</td>
<td>0.1 (-0.2 to 0.3)</td>
<td>0.55</td>
</tr>
<tr>
<td>Dietitian</td>
<td>20,662 (155)</td>
<td>180 (126 – 254)</td>
<td>0.1 (-0.04 to 0.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>Psychologist/mental health professional</td>
<td>17,769 (127)</td>
<td>368 (240 – 605)</td>
<td>-0.01 (-0.2 to 0.1)</td>
<td>0.87</td>
</tr>
<tr>
<td>Other workforce/service aspects</td>
<td></td>
<td>Proportion of services</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychologist in the service</td>
<td>21,070 (159)</td>
<td>82 %</td>
<td>-1.7 (-3.2 to -0.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>At least one consultant with a CCT in Endocrinology and Diabetes</td>
<td>19,637 (148)</td>
<td>20 %</td>
<td>-0.9 (-2.3 to 0.5)</td>
<td>0.20</td>
</tr>
<tr>
<td>24/7 access to advice from the team</td>
<td>21,029 (158)</td>
<td>44 %</td>
<td>-0.002 (-0.2 to 1.2)</td>
<td>0.10</td>
</tr>
<tr>
<td>Achievement of Best Practice Tariff c</td>
<td>18,492 (134)</td>
<td>74 %</td>
<td>-1.8 (-3.7 to 0.1)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Results derived from linear regression models with a random effect for service adjusted for children’s age, diabetes duration, gender, ethnicity and small-area deprivation. The adjustment also included quadratic and cubic terms for the duration and interaction terms between age and duration. Workforce variables entered separately in the regression models.

a caseload defined as the number of children <19 years with T1D for > 3 months cared for by one whole time equivalent (WTE) healthcare professional. WTE refers to contracted work for paediatric diabetes care.

b total staff includes paediatric diabetes specialist nurses, consultants and other fully trained doctors, psychologists or mental health professionals, dietitians, and diabetes educators.

c only in England
Figure 21. Association between diabetes team (total staff) caseload and glycaemic control of children with type 1 diabetes by diabetes duration status.

Results derived from a linear regression model with a random effect for clinic adjusted for children’s age, diabetes duration, gender, ethnicity and small-area deprivation.
6.4 Discussion

Findings of the workforce survey showed wide variations in staffing levels between the four UK nations and revealed some important gaps in key areas of paediatric diabetes services. England had the best staffed paediatric diabetes services with quite evenly distributed workforce between the ten regional diabetes networks. On the other hand, Wales and Northern Ireland appeared to have the lowest ratio of total staff to patient with heavy caseloads, especially for dietitians and psychologists.

An important finding from the current survey was that four out of five services in the UK had a dedicated psychologist working as a member of the multidisciplinary team. This is a notable improvement compared to previous years; for example, previous surveys in 2002 and 2008 had shown that only about one in five clinics provided access to psychological services (35, 123). However, important deficiencies in psychological support still exist in Wales, where less than one in three services had a psychologist working in the team. It is possible that services in England have been able to use funding from the Best Practice Tariff to appoint mental health professionals, but this is not still available in Wales. Both the National Service Framework (96) and NICE guidelines (19) emphasise the importance of providing access to specialised support from mental health professionals in all children with diabetes. Guidelines from the International Society for Paediatric and Adolescent Diabetes (ISPAD) state that the multidisciplinary diabetes team should include a mental health professional who should be able to screen and evaluate psychosocial functioning in relation to diabetes management (126).
The role of psychological services in children’s glycaemic control was also investigated in the linkage analysis with national audit data in England and Wales. Having a psychologist as an integral member of the diabetes team was associated with improved glycaemic control, especially among non-white children with T1D. In fact, non-white children who attended a clinic with a psychologist had, on average, lower HbA1c levels by 4 mmol/mol as compared to non-white children without access to a psychologist. However, there was a great deal of uncertainty around this estimate as reflected by the wide confidence intervals and this finding needs to be further examined in larger samples. In any case, non-white children with T1D in the UK have poorer glycaemic control (127), and this finding seems to suggest that provision of psychological support to this group of children might help reduce ethnic inequalities to some extent.

Another interesting finding was that less than half of the paediatric diabetes services offered 24-hour access to support from members of the multidisciplinary team. This proportion remains the same since 2008 (123) which is quite concerning given the complex nature of diabetes management and the need for ongoing support. As emphasised by the 2015 NICE guidelines, provision of 24-hour support to all children and their families should be essential to the future provision of paediatric diabetes services. Another finding was that less than one in five consultants working in the paediatric diabetes services specialised in endocrinology and diabetes. Even though the proportion of specialised consultants in the UK is still small, it has almost doubled since 2008 (123), indicating an increasing trend towards specialisation of consultant paediatricians.
Nursing staffing levels varied considerably both between the UK countries and within England. At the national level, there were 73 patients per 1 diabetes specialist nurse. A comparison of current findings with that of previous surveys indicates a substantial improvement in nursing caseloads in the UK over the last years, down from 147 patients per nurse in 2002 (35) and 92 patients per nurse in 2008 (123). However, even with this improvement in nursing caseloads, approximately half of the UK diabetes services failed to meet the Royal College of Nursing recommended ratio of $>1:70$ (124). The nursing caseload was even heavier in Northern Ireland where one WTE nurse was responsible for $>100$ patients, although this was compensated by the relatively higher number of diabetes educators who are responsible for the structured education program, an activity typically provided in the UK by diabetes specialist nurses.

In the individual-level analysis focusing on children with T1D in England and Wales, heavier caseloads for the whole diabetes team were associated with poorer glycaemic control. However, the magnitude of the association was relatively small in the general population and therefore was of little clinical significance. As opposed to total staffing levels, profession-specific staffing levels appeared to have no association with children’s glycaemic control. This suggests that the intensity of workforce input provided by the whole diabetes team might be more important as opposed to individual professional input. Two other small-scale UK studies also found no association of glycaemic control with nursing (33, 36) and consultant caseload (36). An effective multidisciplinary team needs more than just an independent contribution of different members, and it is possible that other team factors are important for diabetes outcomes, including skill-mix, team cohesiveness, and consistency of target setting (128).
A heavier caseload had a greater negative impact on glycaemic control for children with longer diabetes duration. The effect of caseload was not observed in those with a shorter duration of diabetes. The observed association between bigger workforce and better glycaemic control in children with longer duration of diabetes might be partially influenced by the collinearity between duration and age, thereby reflecting the fact that adolescents represent a more demanding group requiring more staff time for their care. Although this needs further investigation, this observation may relate to a greater intensity of effort and a prioritisation towards children newly diagnosed with diabetes, possibly at the expense of those with a longer duration. Another explanation could be that during the early stages of the disease, where production of endogenous insulin takes place, the role of the diabetes team is less crucial. The trajectory of higher HbA1c with increasing diabetes duration in clinics with a greater caseload is likely to result in increased risk of vascular diseases. Hence this suggests a need to review and reallocate resource and workload to meet the needs of all children regardless of where they are in the life course of their diabetes.

The survey achieved a high response rate (93%) with a good external validity (i.e. generalizability). However, some potential limitations need to be addressed. First, workforce data were reported by lead consultants, and it is possible that some services might have over- or underestimated their responses in terms of staffing levels or other workforce features. Second, as part of the current survey, no information was collected on transitional diabetes care. Given that most young people above the age of 19 with diabetes will be under adult care, findings of the current survey are unlikely to apply to this age group, and a separate survey will be needed to address needs for this specific population. Finally, the current analysis was based on a cross-sectional analysis of staffing levels at a single time point and, therefore, cannot evaluate changes of staffing
levels across time, address the impact of quality improvement initiatives on paediatric diabetes workforce, or suggest a causal link with glycaemic outcomes.

6.4.1 Conclusion

In conclusion, staffing levels of paediatric diabetes services varied considerably across the UK, with heavy caseloads for psychologists and dietitians in Northern Ireland and Wales. Half of the services met the recommended staffing levels for nurses, and significant gaps were observed in the provision of 24/7 access to advice from the diabetes team. In England and Wales, heavier total staff caseloads for the diabetes team were found to be weakly associated with poorer glycaemic control, with the association being stronger in children with longer duration of T1D. Profession-specific staffing levels were not directly related to children’s glycaemic control.
Chapter 7  Between-clinic variation in children’s glycaemic control: How does the UK compare internationally in type 1 diabetes?

7.1 Introduction

T1D has long been considered as a condition which exemplifies how national health systems perform in response to chronic diseases (129). This is because management of T1D requires complex contributions from different elements of a healthcare system, including continuing patient education, availability and access to appropriate treatment, and coordinated input from multidisciplinary teams. There is clear evidence that achievement of optimal metabolic control, as measured by levels of glycated haemoglobin (HbA1c), is essential in reducing the risk of vascular complications in children with T1D (16). In response to the above evidence, national and international guidelines have proposed particular standards of diabetes care and recommended target HbA1c levels < 48-58 mmol/mol (6.5-7.5%) (19, 130-132). However, a sizable proportion of children with T1D in the UK and other Western countries still fail to achieve optimal glycaemic control within the above targets.

So far, analyses of between-centre variation in childhood T1D outcomes have been typically conducted within individual countries, in most cases reporting considerable clinic differences in glycaemic control (38, 43, 47). International comparison studies looking at differences in glycaemic control between centres have predominantly focused on comparing whole country mean or median HbA1c levels (133, 134), therefore concealing potential within-country variations. Moreover, existing international studies looking at between-clinic variations have focused on crude centre comparisons (135) or on comparisons between selected centres that are not
representative of their respective countries (49, 50, 136). Therefore, exactly how between-centre variation in glycaemic control differs across countries remains an important unanswered question. Similarly, variation within each centre is of interest, as consistently good results should be aimed for.

7.1.1 Aims

This chapter aims to gain a broader perspective of clinic variation in children’s glycaemic control in England and Wales by drawing comparisons with comparable, high-income countries in Western Europe and the USA. More specifically, the chapter’s objectives were: (1) to describe the magnitude of variation in children’s glycaemic control between countries as well as between clinics within countries; (2) to determine how much of the total variation in children’s glycaemic outcome is attributable to clinic differences in each country; (3) to examine cross-country differences in the relationship between within clinic variation and children’s glycaemic control, and (4) to examine whether differences in country mean glycaemic levels persist after controlling for children’s case-mix characteristics and clinic differences.

7.2 Methods

7.2.1 Study design

For the current project, data from six registries and audits already collecting data on children with T1D were used. The above six registries/audits represented eight countries: England and Wales from the National Paediatric Diabetes Audit (NPDA) (137), Sweden from the Swedish Paediatric Diabetes Quality Registry
(SWEDIABKIDS) (47), Denmark from the Danish National Diabetes Registry (DanDiabKids) (138), Norway from the Norwegian Childhood Diabetes Registry (NCDR) (139), Germany and Austria from the Prospective Diabetes Follow-up Registry (DPV) (140), and USA from the T1D Exchange (T1DX) (141). All registries and audits were representative of their respective national population of children with T1D (i.e. coverage of >80% of the population), except T1DX which was a clinic-based registry. A detailed description of included registries/audits is provided in Appendix D.

The current analysis included children <18 years of age who had been diagnosed with T1D and had at least one HbA1c measurement during 2013 (apart from England and Wales where the audit cycle covered the period from April 2013 to March 2014). The following exclusion criteria were applied: newly diagnosed children with less than three months duration of diabetes, children with missing information on case-mix adjustors, children attending small clinics treating less than ten children, and children who changed clinic over the study period. The final sample consisted of 64,666 children with T1D across 528 clinics from eight countries. A flowchart describing in detail the selection of the study population is shown in Figure 22. The current study was approved by ethics committees and appropriate authorities in all participating countries.

### 7.2.2 Outcome measure

The outcome of interest for the current analysis was children’s glycaemic control. This was assessed by plasma levels of HbA1c. All registries reported HbA1c in mmol/mol in accordance with the International Federation of Clinical Chemistry (IFCC) (107).
Most countries provided all available HbA1c measurements for each child over the study period, in which case the median value was used for the analyses; however, two countries provided a single HbA1c measurement for each child (first registered measurement in Norway and measurement nearest to the child’s date of birth in Denmark). HbA1c measurements are reported in IFCC units (mmol/mol) together with DCCT units (%) in brackets.
Figure 22. Selection of study population

Children <18 years with type 1 diabetes for ≥3 months with at least one HbA1c measurement during 2013/14
N= 66,071 (559 centres)
Austria: 1,583 (19 centres), Denmark: N=1,894 (19 centres), England: 21,401 (163 centres), Germany: 20,187 (216 centres), Norway: 2,321 (26 centres), Sweden: 6,524 (43 centres), US: 10,877 (59 centres), Wales: 1,284 (14 centres)

Missing values in case-mix variables
N=718
England=430, Sweden=268, US=18, Wales=1, Denmark=1

Children who changed clinic during the study period
N= 539
Germany=286, England=209, Sweden=51, Austria=6, Wales=1

Centres with <10 children
N= 134 (31 centres)
Austria=6 (1 centre), Denmark=16 (3 centres), England=11 (2 centres), Germany=81 (20 centres), Norway=6 (1 centre), Sweden=1 (1 centre), US=13 (3 centres)

Final sample
N= 64,666 (528 centres)
Austria=1,571 (18 centres), Denmark=1,877 (16 centres), England= 20,751 (161 centres), Germany= 19,820 (196 centres), Norway=2,315 (25 centres), Sweden= 6,204 (42 centres), US=10,846 (56 centres), Wales=1,282 (14 centres)
7.2.3 Case-mix adjustment

All models were adjusted for four clinically important glycaemic determinants; these included children’s gender, age (<6 years, 6 to <12 years, and 12 to 18 years), duration of diabetes (<2 years, 2 to <5 years, and ≥ 5 years) and minority status (binary variable; yes/no). Since all the above individual factors are outside the control of the clinic environment, the adjustment ensures a fairer comparison between diabetes clinics. Definition of minority status was based on children’s or parent’s country of birth or on children’s self-declared ethnicity status (see Table 14). Finally, the association between diabetes duration and HbA1c was allowed to vary across age categories by the inclusion of age-duration interaction terms.

7.2.4 Statistical analysis

Statistical analysis was conducted in three stages. The first stage of the analysis included the use of country-specific, fixed effect models adjusted for case-mix. These models were used to obtain clinic estimates of adjusted mean HbA1c levels using established methodology (142). Clinic estimates obtained from the above models are similar to comparing clinics in each country as if they had the same case-mix profile of children in terms of gender, age, duration of diabetes, and minority status. Variation between adjusted clinic means across the eight countries was illustrated by constructing box-and-whisker plots. In these plots, the distance between the top and the bottom of the box captures the middle 50% of the clinics in each country. Additionally, the difference in adjusted HbA1c levels between clinics in the highest and lowest decile of each country’s distribution (i.e. middle 80% range) was calculated and presented.
In the second stage of the analyses, a series of country-specific, case-mix adjusted multilevel models with a random effect for clinic were fitted. Use of random effect (multilevel) models allowed the decomposition of the total variation in glycaemic control into two components (i.e. within and between clinics) and the subsequent calculation of the proportion of total variation in the outcome that is attributable to differences between centres (Intraclass Correlation Coefficient - ICC = \frac{\text{between centre variance}}{\text{total variance}}) (143). ICC provides essential information about how achievement of glycaemic control is distributed within a country and helps determine the scope for glycaemic improvements if policy efforts are exclusively focused on narrowing clinic differences (143). The above country-specific, random effect models were extended by introducing the standard deviation of HbA1c values of all children attending a specific centre (HbA1c-SD) as a clinic-level characteristic. The HbA1c-SD represents the average deviation of a child from its clinic mean and provides an indicator of how consistent the glycaemic performance of the diabetes clinic is. Because clinic variability might be related to the size of the clinic, all models were simultaneously adjusted for clinic volume. Country-specific HbA1c-SD regression coefficients were extracted and pooled by random effects meta-analysis.

In the third stage, a pooled analysis was conducted including children from all eight countries. In the pooled dataset, a case-mix adjusted model with a random effect for clinics was fitted, and country was entered as a fixed effect. The pooled analysis aimed to explore whether glycaemic differences across countries persist after controlling for centre effects and differences in the case-mix profile of children across countries.

Parameters in random effects models were estimated using the maximum likelihood method. Model fit was examined by using the likelihood ratio test (LRT). Distribution
of individual and clinic-level residuals was checked in all models and showed approximate normality. A p-value of less than 0.05 was considered statistically significant. Statistical analysis for the specific project was conducted in collaboration with the statistician Julia Hermann from University of Ulm, Germany. Analyses were performed using Stata version 13 and SAS version 9.4.

7.2.5 Sensitivity analysis

To explore whether the differences in the definition of minority status between countries could affect the results, analyses were repeated after exclusion of minority status from case-mix adjustment.

7.3 Results

Characteristics of children and diabetes clinics in each of the eight countries are presented in Table 14 and Table 15 respectively. Gender and age profile of children was relatively similar across all eight countries. Mean duration of diabetes was lowest in Germany and Austria (4.6 years) and highest in the USA (5.7 years). Minority status varied substantially between countries from <10% in Denmark, Norway, and Wales to 27-28% in Austria and England. Achievement of the International Society of Paediatric and Adolescent Diabetes (ISPAD) HbA1c target of <58 mmol/mol (7.5%) varied from 17% in Wales to almost 50% in Sweden.

Figure 23 and Figure 24 show different visualisations of clinic variation in each of the eight countries after adjustment for patient characteristics. Also, Table 16 shows the glycaemic difference between centres in the highest and lowest decile of their country’s distribution. There was a 1.2-fold variation in national mean levels of HbA1c.
across countries from 59 mmol/mol (7.6%) in Sweden to 72 mmol/mol (8.8%) in Wales. Clinic variation was lowest in Sweden and Norway; in both countries, the difference in case-mix adjusted mean HbA1c between clinics in the lowest and highest decile was 6-7 mmol/mol (0.6%). Although Germany and Austria had among the lowest mean HbA1c values, they both showed the largest within-country variations with clinics in the highest decile of the country distribution having higher glycaemic levels by more than 14 mmol/mol (1.3%) as compared to clinics in the lowest decile.

In addition to absolute differences between clinics, Table 16 also shows the proportion of the total variation in HbA1c that is attributable to between-clinic differences in each country after controlling for children characteristics. In most countries, adjusted ICCs were small, indicating that clinics had a limited impact on children’s glycaemic outcomes. However, adjusted ICCs showed a 9.3-fold variation across countries, ranging from ≤4% in Nordic countries to ~15% in countries like Germany and Austria. England, Wales, and the US showed a middle-range ICC (i.e. 5-8%). Exclusion of minority status from adjustment had a minimal impact on clinic variations in most countries. The only exception was the US, where exclusion of minority status resulted in a reduction in ICC from 7.9% to 6.6%.
Table 14. Description of data sources and participant characteristics

<table>
<thead>
<tr>
<th>Country</th>
<th>Registry/Audit</th>
<th>National coverage</th>
<th>HbA1c completeness (a), %</th>
<th>No of children (clinics)</th>
<th>Male, %</th>
<th>Age, years (b)</th>
<th>Diabetes duration, years (b)</th>
<th>Minority status-definition</th>
<th>Minority status-achievement, %</th>
<th>HbA1c(b), mmol/mol</th>
<th>%</th>
<th>ISPAD target (c) achievement, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden</td>
<td>SWEDIABKIDS</td>
<td>~98%</td>
<td>~100</td>
<td>6,204 (42)</td>
<td>53</td>
<td>12.2 (4.0)</td>
<td>4.7 (3.7)</td>
<td>Patient born outside of Sweden</td>
<td>13</td>
<td>59 (13)</td>
<td>7.6 (1.2)</td>
<td>49</td>
</tr>
<tr>
<td>Germany</td>
<td>DPV</td>
<td>~95%</td>
<td>98</td>
<td>19,820 (196)</td>
<td>52</td>
<td>12.0 (3.9)</td>
<td>4.6 (3.6)</td>
<td>Patient or at least one parent born outside of Germany/Austria</td>
<td>20</td>
<td>61 (15)</td>
<td>7.7 (1.4)</td>
<td>46</td>
</tr>
<tr>
<td>Austria</td>
<td>DPV</td>
<td>~80%</td>
<td>99</td>
<td>1,571 (18)</td>
<td>55</td>
<td>11.9 (4.0)</td>
<td>4.6 (3.7)</td>
<td>Patient or at least one parent born outside of Germany/Austria</td>
<td>28</td>
<td>62 (16)</td>
<td>7.8 (1.4)</td>
<td>43</td>
</tr>
<tr>
<td>Denmark</td>
<td>DanDiabKids</td>
<td>~100%</td>
<td>91</td>
<td>1,877 (16)</td>
<td>51</td>
<td>12.7 (3.6)</td>
<td>5.1 (3.6)</td>
<td>Both parents born outside of Denmark</td>
<td>8</td>
<td>64 (16)</td>
<td>8.0 (1.5)</td>
<td>38</td>
</tr>
<tr>
<td>Norway</td>
<td>NCDR</td>
<td>&gt;95%</td>
<td>96</td>
<td>2,315 (25)</td>
<td>52</td>
<td>12.7 (3.7)</td>
<td>5.2 (3.5)</td>
<td>Mother born outside of the Nordic countries</td>
<td>6</td>
<td>66 (14)</td>
<td>8.2 (1.3)</td>
<td>29</td>
</tr>
<tr>
<td>England</td>
<td>NPDA</td>
<td>&gt;95%</td>
<td>95</td>
<td>20,751 (161)</td>
<td>52</td>
<td>12.4 (3.8)</td>
<td>4.7 (3.7)</td>
<td>Any non-white ethnicity</td>
<td>27</td>
<td>71 (18)</td>
<td>8.6 (1.6)</td>
<td>20</td>
</tr>
<tr>
<td>USA</td>
<td>T1D Exchange</td>
<td>N/A</td>
<td>83</td>
<td>10,846 (56)</td>
<td>52</td>
<td>12.6 (3.5)</td>
<td>5.7 (3.5)</td>
<td>Other than non-Hispanic white ethnicity</td>
<td>22</td>
<td>72 (17)</td>
<td>8.7 (1.6)</td>
<td>18</td>
</tr>
<tr>
<td>Wales</td>
<td>NPDA</td>
<td>&gt;95%</td>
<td>93</td>
<td>1,282 (14)</td>
<td>52</td>
<td>12.2 (3.7)</td>
<td>4.7 (3.6)</td>
<td>Any non-white ethnicity</td>
<td>5</td>
<td>72 (18)</td>
<td>8.8 (1.6)</td>
<td>17</td>
</tr>
</tbody>
</table>

\(a\) HbA1c completeness defined as the proportion of eligible children in each country having a recorded HbA1c measurement during the study period.

\(b\) Data shown as mean (standard deviation).

\(c\) International Society of Paediatric and Adolescent Diabetes (ISPAD) HbA1c target of <58 mmol/mol (7.5%).

Note: DPV: Prospective Diabetes Follow-up Registry, DanDiabKids: Danish National Diabetes Registry, NPDA: National Paediatric Diabetes Audit, NCDR: Norwegian Childhood Diabetes Registry, SWEDIABKIDS: Swedish Paediatric Diabetes Quality Registry.
<table>
<thead>
<tr>
<th>Country</th>
<th>No of centres</th>
<th>Mean HbA1c %</th>
<th>Mean % male</th>
<th>Mean age (years)</th>
<th>Mean duration of diabetes (years)</th>
<th>% minority status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden</td>
<td>42</td>
<td>7.5 (7.3-7.7)</td>
<td>59 (58-61)</td>
<td>12.3 (12.0-12.7)</td>
<td>4.9 (4.6-5.1)</td>
<td>10 (7-13)</td>
</tr>
<tr>
<td>Germany</td>
<td>196</td>
<td>7.8 (7.4-8.1)</td>
<td>61 (57-65)</td>
<td>12.0 (11.6-12.3)</td>
<td>4.5 (4.0-5.0)</td>
<td>19 (10-28)</td>
</tr>
<tr>
<td>Austria</td>
<td>18</td>
<td>7.8 (7.5-8.3)</td>
<td>62 (59-67)</td>
<td>11.8 (11.3-12.3)</td>
<td>4.5 (4.1-5.1)</td>
<td>25 (16-33)</td>
</tr>
<tr>
<td>Denmark</td>
<td>16</td>
<td>8.1 (7.8-8.3)</td>
<td>65 (62-67)</td>
<td>12.8 (12.5-13.0)</td>
<td>5.1 (4.8-5.5)</td>
<td>6 (3-8)</td>
</tr>
<tr>
<td>Norway</td>
<td>25</td>
<td>8.2 (8.0-8.3)</td>
<td>66 (64-68)</td>
<td>12.7 (12.3-12.9)</td>
<td>5.3 (4.8-5.5)</td>
<td>4 (1-5)</td>
</tr>
<tr>
<td>England</td>
<td>161</td>
<td>8.7 (8.4-8.9)</td>
<td>71 (68-74)</td>
<td>12.4 (12.0-12.7)</td>
<td>4.7 (4.4-5.0)</td>
<td>14 (5-47)</td>
</tr>
<tr>
<td>USA</td>
<td>56</td>
<td>8.7 (8.4-9.0)</td>
<td>71 (68-75)</td>
<td>12.5 (12.2-13.0)</td>
<td>5.7 (5.1-6.2)</td>
<td>16 (10-27)</td>
</tr>
<tr>
<td>Wales</td>
<td>14</td>
<td>8.8 (8.4-9.0)</td>
<td>72 (69-75)</td>
<td>12.3 (11.8-12.4)</td>
<td>4.8 (4.3-5.0)</td>
<td>2 (0-3)</td>
</tr>
</tbody>
</table>
Figure 23. Box-and-whisker plots illustrating how clinic HbA1c vary around national mean values across eight high-income countries.

Note: The shaded box captures the middle 50% of the clinics in each country (Interquartile range-IQR). Whiskers extend to include clinics that lie within 1.5 times the IQR beyond the upper and lower quartile. Clinic means derived from fixed-effect models adjusted for individual gender, age, duration of diabetes, and minority status. Crude national average HbA1c values are shown as red diamonds.
Figure 24. Kernel-smoothed distribution of adjusted clinic HbA1c means by paediatric diabetes registry/audit.

Note: The dashed vertical line shows the International Society of Paediatric and Adolescent Diabetes (ISPAD) glycaemic target recommended for children with diabetes. Clinic means derived from linear fixed effect models adjusted for individual gender, age, duration of diabetes, and minority status.
Table 16. Absolute and relative measures of clinic variation in HbA1c by country after adjustment for patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sweden</th>
<th>Germany</th>
<th>Austria</th>
<th>Denmark</th>
<th>Norway</th>
<th>England</th>
<th>USA</th>
<th>Wales</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c difference</td>
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<td></td>
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<tr>
<td>between centres in</td>
<td>6.0 (0.6)</td>
<td>14.5 (1.3)</td>
<td>15.7 (1.4)</td>
<td>9.8 (0.9)</td>
<td>6.6 (0.6)</td>
<td>11.0 (1.1)</td>
<td>12.8 (1.2)</td>
<td>12.3 (1.1)</td>
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<td>the highest and</td>
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<td>lowest decile -</td>
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<td>mmol/mol (%) a</td>
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<tr>
<td>Proportion of total</td>
<td>4.0%</td>
<td>16.8%</td>
<td>13.9%</td>
<td>4.0%</td>
<td>1.8%</td>
<td>5.5%</td>
<td>7.9%</td>
<td>4.7%</td>
</tr>
<tr>
<td>variation in HbA1c</td>
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<td>attributable to</td>
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<td>differences between</td>
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<td>clinics (ICC-</td>
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<tr>
<td>Intraclass Correlation Coefficient)b</td>
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</tr>
</tbody>
</table>

Results provided by country-specific models adjusted for children’s characteristics with regard to gender, age, duration of diabetes and minority status.

a fixed effect models
b models with a random effect for the centre
The forest plot in Figure 25 shows how the association between clinic HbA1c-SD and children’s glycaemic control varied across the eight countries. As shown, children who attended clinics with larger variation in their glycaemic performance (i.e. higher clinic HbA1c-SD) had, on average, higher HbA1c levels and this positive association was consistently observed across all countries. More specifically, the meta-analysis showed that, overall, there was a deterioration in glycaemic control by 5.6 mmol/mol; (0.5%) for each 5 mmol/mol (0.5%) increase in clinic HbA1c-SD.

Figure 26 shows the mean HbA1c levels in each of the eight countries before and after adjustment for cross-country differences in children characteristics and clinic effects. As shown, glycaemic differences between countries were slightly attenuated after controlling for case-mix and clinic effects. However, the addition of country in the model showed that the country where a child received care was a significant independent determinant of their glycaemic control irrespective of centre and children characteristics (p-value of LRT<0.001).
Figure 25. Random-effects meta-analysis of change in children’s HbA1c levels (mmol/mol) (95% confidence interval) per 5 mmol/mol (0.5%) increase in clinic HbA1c-SD.

Note: A positive association indicates worse glycaemic control in children attending clinics with more variable glycaemic performance. I² statistic quantifies the percentage of total variation in estimates that can be attributed to between-country heterogeneity. Estimates derived from country-specific models with a random effect for centre adjusted for patient characteristics and clinic volume.
Figure 26. Country mean HbA1c before and after adjustment for cross-country differences in children characteristics and clinic effects.

Note: Pooled analysis including data from all eight countries. Estimates derived from a linear regression model with a random effect for clinics adjusted for children’s age, gender, diabetes duration, and minority status.
7.4 Discussion

This chapter has compared unwarranted variations in England and Wales with other similar countries by looking at how HbA1c is distributed within and across eight high-income countries (seven in Europe and the US). Findings from this large international study revealed substantial differences in mean HbA1c between countries as well as between diabetes clinics within countries. More specifically, comparisons of between- and within-country variations in glycaemic achievement revealed three distinctive patterns; First, most children with diabetes in Nordic countries (Sweden, Denmark, and Norway) homogeneously achieved good levels of glycaemic control regardless of the clinic they attend. Second, large clinic variations were observed within Germany and Austria, countries with average glycaemic levels comparable to those of Nordic countries. Third, diabetes clinics in England, Wales, and the US showed low-to-moderate variation around poor national average values. Another interesting finding was that across all countries, children who attended centres with more variable glycaemic results had poorer glycaemic control. Finally, the country where a child received care remained a significant glycaemic determinant even after removing cross-country differences in case-mix characteristics and clinic effects.

Sweden had the lowest mean HbA1c and together with the other Nordic countries showed some of the smallest clinic variations. This suggests that most children with T1D in those countries achieve good levels of glycaemic control regardless of the clinic they attend. Achieving such a homogeneity within a country indicates that clinic variations are not immutable and that there is a potential for improvement in many
countries. Of course, this presupposes that we know the causes of this variation; while this is not possible in the context of the current study, looking at how some countries have succeeded in the area could provide some useful lessons.

In Nordic countries, the collaboration between “quality registries” has been a key effort in stimulating performance improvements in paediatric diabetes care (135). Data from quality registers in those countries provide clinicians with essential information with which to compare performance and facilitate discussion on improvement. Sweden has been particularly successful in establishing a national program of continuous quality improvement in childhood diabetes which is based on transparent public reporting of centre performance, regular monitoring of variations, use of performance indicators as a clinical tool for professional development, and active participation of clinics in quality improvement “collaboratives” (144, 145). This system-wide approach probably accounts, at least to some extent, for the improved glycaemic outcomes in Sweden (144).

Another key point that emerged from the current analysis was that at comparable average levels of glycaemic control, countries showed very diverse levels of clinic variation suggesting that whole-country mean HbA$_1$c levels can conceal important within-country inequalities and are therefore an insufficient aggregate of a country’s glycaemic performance. In fact, a good average glycaemic performance at a national level does not necessarily reflect homogenous distribution within a country. For example, the cross-country analysis revealed large clinic variations in Germany and Austria, countries with average glycaemic levels comparable to those of Sweden and other Nordic countries. In Germany and Austria, almost one-sixth of the total variation in HbA$_1$c was attributable to differences between diabetes clinics. This indicates that
Clinic-based interventions aiming to reduce clinic variation in those countries could have an appreciable impact on improving glycaemic performance at a national level.

Such large clinic variation may be partly related to how diabetes care is organised. Unlike the UK and Nordic countries, where diabetes care is principally provided by secondary care clinics typically serving children and adolescents in their catchment areas, in Germany and Austria, patients can select their own providers from a mixture of public and private practices. Given this open competition, clinics are more likely to exhibit various discretionary policies about the profile of patients they are willing to accept. Similarly, motivated patients may prefer to attend clinics with a good reputation. However, the degree of clinic variation observed in those countries is unlikely to be solely explained by differences in patient preferences or uncaptured case-mix variations.

Since 1995, Germany and Austria have established a comprehensive documentation system for paediatric diabetes care (146, 147). National benchmarking data have been provided to participating paediatric diabetes centres in both countries in anonymised form. However, de-anonymised reports are not openly available to the public (140), thereby compromising their usefulness in addressing unwarranted variations.

Currently, there are no established benchmarking schemes in the USA, where moderate clinic variations were observed. Public reporting of performance indicators in paediatric diabetes care has long been an essential component of the accountability for quality improvement in Nordic countries and since 2012/13 in England and Wales.

There is evidence from other medical specialities that open disclosure of provider performance measures is associated with better performance (148) and has a small impact on patient movements (149). In any case, a climate of shared trust needs to be
cultivated between clinicians and other stakeholders when such policies are implemented in order to avoid defensive behaviours possibly resulting in “cream skimming” or discontinuing of information sharing (150).

The development and implementation of guidelines is another main policy lever to harmonise diabetes practice both within and between countries. A comparative analysis of national paediatric diabetes guidelines across EU countries and Norway showed that although most countries used established national or international guidelines, there was insufficient information on compliance with those guidelines (151). Pay-for-performance incentives (125) and peer-review programme (152) for paediatric diabetes care have been introduced in England in 2012-13 in order to encourage adherence to standards of care, but their contribution to future attainment has yet to be evaluated. Re-allocation of resources (i.e. staffing levels, psychological services, insulin pumps) in order to ensure sufficient supply in remote centres could also be used as a means to promote consistency across diabetes clinics.

Although focusing on policies aiming to narrow clinic variation in paediatric diabetes care should be a key priority, such policies might not be sufficient to address cases where most clinics in a country are not performing optimally. A striking example is that of England and Wales, countries with poor average HbA1c levels and low-to-moderate clinic variation. The cross-country comparisons revealed that some of the best clinics in England and Wales perform poorly when compared even with some of the “worse” Swedish centres. The same pattern also appeared in the US. This suggests that quality improvement in those countries could best be facilitated not only by targeting poor clinics, but also by “shifting the curve” of overall paediatric diabetes practice towards higher levels of quality. In other words, all clinics within the country,
even those that are considered to perform well, should be encouraged to make local changes. The recent changes towards tighter glycaemic targets for all children of <48 mmol/mol (6.5%) in the UK (19) and <58 mmol/mol (7.5%) in the USA (130) might help towards this goal. Patient-centred policies have also been shown to be useful in stimulating whole system improvements. In the case of England and Wales, the recent introduction of patient reported experience measures (PREM) in paediatric diabetes care in 2012/13 is considered an important initiative in engaging patients and families in local decision making. Collection of patient-reported measures is currently being considered in Nordic countries but has not been implemented yet (153, 154).

Across all countries, children attending clinics with more variable glycaemic results had, on average, higher HbA1c. This association also tended to be more marked in countries with larger between-clinic variation. One way of interpreting this finding is that a clinic achieving consistent glycaemic results is likely to reflect a broader organisational culture within diabetes teams in aspects related to goal setting, team cohesiveness and coordination. For example, a previous study from the Hvidore group showed better glycaemic performance in centres where the diabetes team set consistent glycaemic targets (128). Achievement of higher homogeneity within a clinic also requires focusing attention on the management of challenging groups of children, such as adolescents who are more likely to exhibit greater variability in their metabolic control. Taken together, these findings suggest that, in addition to achieving good overall results, centres should also aim for greater consistency in their glycaemic performance.

Significant differences between countries’ glycaemic levels remained over and above children characteristics and clinic differences. Several factors could contribute to these
differences, including availability and utilisation of insulin pumps, reimbursement schemes, educational programs, training of healthcare professionals, national targets, lifestyle aspects, and impact of low socioeconomic status. All the above aspects of diabetes care could explain some of the differences between countries. However, the connection with glycaemic outcomes is not always straightforward. For example, a previous international comparison study showed that even though use of insulin pumps was much lower in England and Wales (14%) as compared to the USA, Germany, Austria (>40%), differences in insulin delivery method could not adequately explain observed differences in glycaemic control between countries (155). Cross-country comparisons in T1D also need to be interpreted in the light of broader policies in other sectors such as employment, education, and housing, where the product of health is not a primary goal. For example, Nordic countries are widely perceived as homogeneous countries that share a comparable approach to social welfare with an increased emphasis on equality (156).

There are obvious limitations to this study. First, the case-mix adjustment was limited to availability of comparable data across registries. It is likely that unmeasured factors such as the prevalence of diabetes-related comorbidities, and other socioeconomic factors might systematically vary between clinics and thus explain some of the observed variations. Second, a combination of fixed and random effect models was used in the analysis of international data. Although fixed effect models lack the specificity of random effect models, they have been shown to be more sensitive in detecting outliers (157). Therefore, the use of both models reflected an effort to draw a balance between sensitivity and specificity. Third, although an IFCC standardisation scheme was used for all HbA1c measurements in this study, it is still likely that differences in laboratory methods across counties might have contributed to the
observed variations. Fourth, glycaemic data from the USA were based on specific clinics and might not be directly comparable with that of the European population-based registries. Fifth, exclusion of small centres treating less than ten children from the cross-country analysis might have resulted in an underestimation of clinic variations in countries with a large number of small centres such as Germany. Sixth, it is unclear whether differences in the definition of minority status between countries have anyhow affected the results. In any case, however, exclusion of minority status from case-mix adjustment had only a minimal impact on the findings. In the USA, larger clinic variations were masked by failing to control for minority status; such a result could occur, for instance, when poorly performing clinics have fewer minority children who tend to have poorer glycaemic control as compared to non-Hispanic whites (158). Finally, this study was cross-sectional, and as such, it cannot address any causal link between quality improvement initiatives or policies and glycaemic performance.

7.4.1 Conclusion

The current chapter helped gain a broader perspective of clinic variations in England and Wales by drawing useful comparisons with other high-income countries. Findings of this chapter challenge the traditional focus of international T1D benchmarking studies on whole-country averages, which can conceal significant within-country variations. Since the included countries have similar economic structures, findings of this chapter highlight unacceptably large differences in diabetes outcomes. Only by making such differences visible can a discussion be initiated on how outcomes be improved.
Results provide useful opportunities for cross-country learning and have a strong policy relevance in that they can help national registries target their resources to most efficiently improve outcomes. In Nordic countries, the establishment of collaboration between quality registries along with an increasing emphasis on transparency in centre performance have been a significant effort in promoting performance improvement in paediatric diabetes. A relative lack of transparency might explain the wider variations observed in countries like Germany and Austria. In these countries, targeted interventions aiming to reduce centre variability could have an appreciable impact on glycaemic outcomes. In countries with high average HbA1c levels and low-to-moderate centre variations such as England, Wales, and the USA, some of the ‘best’ clinics are performing sub-optimally when compared even with the ‘worst’ Swedish clinics. This suggests that quality improvement might best be achieved not only by narrowing clinic variation but also by policies aiming to stimulate whole-system improvements.
Chapter 8  Time trends in mean glycaemic control and centre variation for children with type 1 Diabetes in England and Wales from 2005 to 2014

8.1 Introduction

So far, the study of centre variation around national average HbA$_1c$ levels in England and Wales has focused on cross-sectional analyses of national audit data. Although these snapshot analyses have provided opportunities for in-depth and insightful exploration of the national data, they are inherently limited since they cannot capture the dynamic nature of glycaemic achievement at the national level and its changes across time.

Findings provided by the NPDA have demonstrated that the mean HbA$_1c$ for CYP in England and Wales has remained mostly unchanged at about 9% over the period from 2004 to 2012. Moreover, NPDA findings have revealed that one out of four children had poor glycaemic control [HbA$_1c$ >80mmol/mol (9.5%)], while at the same time less than one in five children met the NICE recommended a glycaemic target of HbA$_1c$ <58 mmol/mol (7.5%) (14). Results on diabetes care processes also highlight the gaps in services across England and Wales, with only 6.7% of children above the age of 12 receiving all NICE recommended care processes in 2011 and even though this percentage has increased from 2004, it remains surprisingly low and compares unfavourably with the same percentage in adults (60.5% in 2011).
In 2012, the National Paediatric Diabetes Service Improvement Delivery Plan set a target to decrease national average levels of HbA1c in England and Wales by 16 mmol/mol (1.5%) by 2023 and also narrow clinic variations (105). Since 2012, the NPDA has reported some improvements in the crude national average HbA1c levels, but findings are based on cross-sectional data which preclude a robust analysis of time trends in national HbA1c levels. It also remains unclear whether these improvements have been accompanied by a reduction in clinic variation which, by itself, constitutes an equally desirable outcome.

8.1.1 Aims

The current chapter will, therefore, use an extension of the multilevel methodology used in previous chapters to analyse data from the NPDA for the period 2005-2014 with the aim of exploring (1) how the mean glycaemic control of children and adolescents with T1D has changed over the last decade in England and Wales after adjustment for covariates, and (2) how variation in HbA1c between diabetes services has changed over the same period.

8.2 Methods

8.2.1 Study design

The current study is based on NPDA data covering nine audit years from 2005/06 to 2014/15. For administrative reasons, data from the 2010/11 audit year could not be individually linked to the national cohort and therefore were not included in the current analysis. Patients were eligible for inclusion in the study if they met the following criteria: children and adolescents <19 years who were diagnosed with T1D for at least
three months, had documented at least one HbA\textsubscript{1c} measurement over the period from 1\textsuperscript{st} April 2005 to 31\textsuperscript{st} March 2015, and had available data on gender, age, date of diagnosis, and clinic. Three hundred and forty nine children were excluded because they had missing data on clinic identification and 343 children were excluded because of missing data on gender, age or date of diagnosis. For children who changed clinic over the study period (n=1,769), only HbA\textsubscript{1c} measurements from clinics where children were treated for longer were analysed. In case children spent equal time between clinics, data from the most recent clinic were included in the analysis.

The number of recorded HbA\textsubscript{1c} measurements differed across the audit years, from only one yearly measurement during the first five years (i.e. 2005/06 to 2009/10) to all recorded measurements in the most recent years (2011/12 to 2014/15). The mean number of HbA\textsubscript{1c} measurements per patient per year ranged from 2.5 (2011/12) to 4.1 (2014/15). To keep consistency across the whole study period, the median HbA\textsubscript{1c} measurement per audit year for each patient was used in the final analysis dataset. HbA\textsubscript{1c} measurements are reported in IFCC units (mmol/mol) together with DCCT units (%) in brackets.

Participating clinics reached a 100% national coverage in 2012/13 (n=176). Sixty-three out of 176 clinics (i.e. 36%) provided data across all audit years. The final study population included 322,691 HbA\textsubscript{1c} measurements from 41,860 children and adolescents across 176 clinics. HbA\textsubscript{1c} measurements are reported in IFCC units (mmol/mol) with DCCT units (%) shown in brackets.
8.2.2 Statistical analysis

Data on HbA1c were analysed using a three-level hierarchical regression model with measurement occasions at level 1, individuals as level 2, and diabetes centres at level 3. Audit year (centred on the year 2009) was used as the time metric for the current analysis. A quadratic and cubic term for audit year significantly improved model fit and were included in the fixed part of the model. The following covariates were also added in the fixed part of the model: age (in years), age^2, gender, and age at diagnosis (4 categories; <5 years, 5 to <10 years, 10 to <15 years, and ≥15 years). Interaction terms between age and duration categories significantly improved model fit and were retained in the model. The linear and quadratic terms for audit year were added in the random part of the model at both level 2 (individual level) and level 3 (clinic level). This allowed the between-individual and between-clinic components of the variance to depend on time (i.e. audit year). A cubic term of audit year was only imposed as a fixed effect to avoid unnecessary complexity in the model. Parameters of the random part of the model were used to calculate the Variance Partitioning Coefficient (VPC) as a function of audit year. VPC represents the proportion of the total variation in HbA1c that is attributable to between-clinic differences (i.e. variation). Mathematical notations of the multilevel model are provided in Appendix E.

Statistical analyses were performed using Stata v.13 and MLwiN v2.33. In terms of descriptive statistics, continuous variables were presented as mean and standard deviation or median and interquartile range depending on their distribution. For categorical data, percentages were calculated. In the multilevel model, parameters were estimated by iterative generalised least squares, and goodness of fit was assessed by -2 log likelihood with smaller values indicating a better fit. In the multilevel model,
an unstructured covariance matrix was used to allow for flexibility in the correlation between intercepts and slopes. Continuous variables were centred around their mean value, and categorical variables were added as dummy variables taking values of either 1 (representing membership) or 0 (representing non-membership). Comparison between subsequently fitted nested models was made using the deviance (Likelihood Ratio) chi-squared test at the significance level of 0.05.

8.2.3 Sensitivity analyses

Two sensitivity analyses were conducted. First, analyses were repeated in a subsample of the national cohort with available data on ethnicity and deprivation (n=37,684) to examine time trends in HbA1c and clinic variation after adjusting for these additional variables. Second, analyses were repeated in the sub-cohort of 63 diabetes clinics that provided data across the whole 10-year period. This analysis was conducted to explore the potential impact of low clinic participation on clinic variation over the first years of the study period.

8.3 Results

8.3.1 Descriptive findings

Overall, 41,860 children and adolescents <19 years with T1D across 176 clinics were included in the analyses. The number of patients (clinics) per audit year increased from 8,764 (89) in 2005/06 to 24,649 (176) in 2014/15. A total of 19,688 were female (47%). Median age at diabetes onset was 8.5 years (IQR 4.8 to 11.7). Table 17 presents characteristics of children by audit year. As shown, the gender and diabetes duration profile of children was quite similar across the years. Age distribution of children was
slightly shifted towards older ages, especially during the last two years. Moreover, the percentage of non-white children was slightly smaller during the first years as compared to most recent audit years (~15% vs ~19%). The boxplots in Figure 27 show the spread of crude clinic HbA1c values over the whole study period.
Table 17. Characteristics of children and number of centres by audit year (2005/06 to 2014/15)

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of children</td>
<td>8,764</td>
<td>9,660</td>
<td>10,423</td>
<td>12,744</td>
<td>15,346</td>
<td>20,512</td>
<td>22,137</td>
<td>24,025</td>
<td>24,649</td>
</tr>
<tr>
<td>Number of centres</td>
<td>89</td>
<td>99</td>
<td>103</td>
<td>119</td>
<td>145</td>
<td>171</td>
<td>176</td>
<td>176</td>
<td>176</td>
</tr>
<tr>
<td>HbA1c(^a) (mmol/mol)</td>
<td>75 (18)</td>
<td>75 (19)</td>
<td>75 (20)</td>
<td>75 (19)</td>
<td>75 (18)</td>
<td>73 (17)</td>
<td>72 (18)</td>
<td>71 (18)</td>
<td>70 (18)</td>
</tr>
<tr>
<td>HbA1c(^a) (%)</td>
<td>9.0 (1.7)</td>
<td>9.0 (1.7)</td>
<td>9.0 (1.8)</td>
<td>9.0 (1.7)</td>
<td>9.0 (1.7)</td>
<td>8.8 (1.6)</td>
<td>8.8 (1.6)</td>
<td>8.7 (1.6)</td>
<td>8.5 (1.6)</td>
</tr>
<tr>
<td>Age (years) (^b)</td>
<td>13.4 (10.1-15.6)</td>
<td>13.1 (9.9-15.5)</td>
<td>13.1 (10.0-15.6)</td>
<td>13.1 (10.2-15.6)</td>
<td>13.2 (10.3-15.5)</td>
<td>13.2 (10.1-15.4)</td>
<td>13.3 (10.0-15.5)</td>
<td>13.5 (10.1-15.8)</td>
<td>13.6 (10.1-16.0)</td>
</tr>
<tr>
<td>Diabetes duration (years) (^b)</td>
<td>4.4 (2.2-7.3)</td>
<td>4.3 (2.0-7.2)</td>
<td>4.4 (2.1-7.4)</td>
<td>4.4 (2.1-7.5)</td>
<td>4.3 (2.0-7.4)</td>
<td>4.3 (2.0-7.4)</td>
<td>4.3 (2.0-7.5)</td>
<td>4.4 (2.0-7.6)</td>
<td>4.4 (2.1-7.7)</td>
</tr>
<tr>
<td>% female</td>
<td>48</td>
<td>48</td>
<td>48</td>
<td>47</td>
<td>47</td>
<td>47</td>
<td>48</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>% non-white</td>
<td>14</td>
<td>15</td>
<td>16</td>
<td>16</td>
<td>15</td>
<td>17</td>
<td>19</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>% missing ethnicity</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
<td>8</td>
</tr>
<tr>
<td>% highest deprivation quintile</td>
<td>16</td>
<td>19</td>
<td>20</td>
<td>19</td>
<td>19</td>
<td>19</td>
<td>20</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>% missing deprivation</td>
<td>14</td>
<td>1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

\(^a\) Presented as mean (standard deviation)

\(^b\) Presented as median (interquartile range)
8.3.2 **Time trends in adjusted mean HbA$_{1c}$**

Results of the multilevel model are presented in Table 18. After adjusting for gender, age, and age at diagnosis, population average HbA$_{1c}$ reduced by 6 mmol/mol over the 10-year period, from 76 mmol/mol (9.1%) in 2005 to 70 mmol/mol (8.5%) in 2014 (see Figure 28). As illustrated in the figure, population average HbA$_{1c}$ reduced over time in a non-linear fashion, with most of the reduction occurring after 2008/09.

![Boxplots showing variation in crude HbA$_{1c}$ between paediatric diabetes centres by audit year (2005 to 2014).](image)

*Note: Shaded boxes represent the interquartile range (IQR) capturing the middle 50% of clinics. Whiskers extend to include all HbA$_{1c}$ values within 1.5 times the IQR beyond the upper and lower quartile. Outlying clinic HbA$_{1c}$ values are not shown.*
Table 18. Results of 3-level hierarchical model analysing time trends in HbA1c levels in children<19 years with type 1 diabetes in England and Wales from 2005 to 2014

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>75.6</td>
<td>0.34</td>
</tr>
<tr>
<td>Year</td>
<td>-0.70</td>
<td>0.08</td>
</tr>
<tr>
<td>Year(^2)</td>
<td>-0.10</td>
<td>0.02</td>
</tr>
<tr>
<td>Year(^3)</td>
<td>0.006</td>
<td>0.002</td>
</tr>
<tr>
<td>Female</td>
<td>1.65</td>
<td>0.15</td>
</tr>
<tr>
<td>Age</td>
<td>1.46</td>
<td>0.04</td>
</tr>
<tr>
<td>Age(^2)</td>
<td>0.07</td>
<td>0.005</td>
</tr>
<tr>
<td>Age at diagnosis &lt;5 yrs (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-&lt;10 yrs</td>
<td>0.64</td>
<td>0.23</td>
</tr>
<tr>
<td>10-&lt;15 yrs</td>
<td>-6.43</td>
<td>0.24</td>
</tr>
<tr>
<td>≥15 yrs</td>
<td>-41.82</td>
<td>4.29</td>
</tr>
<tr>
<td>Age(\times) diagnosis age 5-&lt;10 yrs</td>
<td>0.35</td>
<td>0.05</td>
</tr>
<tr>
<td>Age(\times) diagnosis age 10-&lt;15 yrs</td>
<td>2.25</td>
<td>0.09</td>
</tr>
<tr>
<td>Age(\times) diagnosis age ≥15 yrs</td>
<td>10.48</td>
<td>2.14</td>
</tr>
<tr>
<td>Age(^2)(\times) diagnosis age 5-&lt;10 yrs</td>
<td>-0.12</td>
<td>0.01</td>
</tr>
<tr>
<td>Age(^2)(\times) diagnosis age 10-&lt;15 yrs</td>
<td>-0.27</td>
<td>0.02</td>
</tr>
<tr>
<td>Age(^2)(\times) diagnosis age ≥15 yrs</td>
<td>-0.77</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Between-clinic variances/covariances

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept variance</td>
<td>12.0</td>
<td>1.51</td>
</tr>
<tr>
<td>Year variance</td>
<td>0.80</td>
<td>0.11</td>
</tr>
<tr>
<td>Year(^2) variance</td>
<td>0.02</td>
<td>0.004</td>
</tr>
<tr>
<td>Intercept-year covariance</td>
<td>0.03</td>
<td>0.29</td>
</tr>
<tr>
<td>Intercept-year(^2) covariance</td>
<td>-0.19</td>
<td>0.06</td>
</tr>
<tr>
<td>Year-year(^2) covariance</td>
<td>-0.10</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Between-individual variances/covariances

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept variance</td>
<td>219.7</td>
<td>2.32</td>
</tr>
<tr>
<td>Year variance</td>
<td>7.37</td>
<td>0.13</td>
</tr>
<tr>
<td>Year(^2) variance</td>
<td>0.30</td>
<td>0.008</td>
</tr>
<tr>
<td>Intercept-year covariance</td>
<td>4.72</td>
<td>0.39</td>
</tr>
<tr>
<td>Intercept-year(^2) covariance</td>
<td>-5.30</td>
<td>0.11</td>
</tr>
<tr>
<td>Year-year(^2) covariance</td>
<td>-0.55</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Within-individual variance 83.94 0.45

-2Log-likelihood 1185695
Figure 28. Adjusted mean HbA1c (95% CI); 2005 to 2014.

Note: Population average HbA1c by audit year, plotted using the parameters from a three-level hierarchical regression model adjusted for gender, age, age^2, and age at diagnosis as fixed effects. The model included a linear, quadratic and cubic term for audit year as fixed effects. The linear and quadratic terms for audit year were also added in the random part of the model at both individual and centre level.
8.3.3 Changes in clinic variation over time

Analysis of the variance components in HbA\textsubscript{1c} showed that over the 10-year period, the proportion of total variance in HbA\textsubscript{1c} at the level of the clinic decreased from 9.4% in 2005 to just below 4% in 2014, representing a 60% reduction (see Figure 29). Most of the reduction in the proportion of total variance at the clinic level occurred over the first four years. After 2008, the proportion remained stable at around 4% until the end of the study period.

![Figure 29. Proportion of total variance in HbA\textsubscript{1c} at the level of the clinic by audit year, 2005/06-2014/15](image)

*Note: Results from a three-level hierarchical regression model adjusted for gender, age, age\textsuperscript{2}, and age at diagnosis. The model included a linear, quadratic and cubic term for audit year. Linear and quadratic terms for audit year were added in the random part of the model at both individual and clinic level.*
8.3.4 Sensitivity analyses

Two sensitivity analyses were conducted. First, analyses were repeated in a subsample of the national cohort including 37,684 children with available data on ethnicity and deprivation. This analysis provided similar results in both mean HbA$_{1c}$ and variance parameters to those of the initial cohort (see Appendix F). The second sensitivity analysis included data from the 63 clinics which participated throughout the 10-year period (n=16,921) (see Appendix G). Results of this analysis showed a very similar pattern of change in the population average HbA$_{1c}$ value. The sensitivity analysis also showed that the proportion of total variance in HbA$_{1c}$ at the clinic level followed a similar pattern of change as compared to that of the national cohort, however showing a smaller reduction over the 10-year period (41% vs 60%).

8.4 Discussion

Analysis of national audit data of 41,860 children and adolescents with T1D in England and Wales showed that HbA$_{1c}$ levels have decreased by 6 mmol/mol over the last decade from 76 mmol/mol (9.1%) in 2005 to 70 mmol/mol (8.6%) in 2015. Moreover, the proportion of the total variation in HbA$_{1c}$ at the clinic level has dropped from 9.4% to around 4% over the same period.

The drop of the national HbA$_{1c}$ levels by 6 mmol/mol (0.6%) represents an 8% improvement in national glycaemic achievement for children and adolescents with T1D over the last decade. This is a clinically meaningful change since findings from the DCCT have shown that a reduction in HbA$_{1c}$ at the range of 10% confers a 43% reduction in the risk of microvascular complications such as retinopathy and macroalbuminuria. The rate of improvement in national glycaemic achievement has
exceeded that observed in other similar European countries. For example, in Germany and Austria national HbA1c levels have decreased from 8.7% to 8.1% over a 14-year period (1995 to 2009) (42). Other countries like Denmark have also experienced quite comparable improvements in glycaemic control, with the average HbA1c falling from 9.1% to 8.2% over a 9-year period (1997 – 2006) (48).

Analysis of time trends in mean HbA1c levels and clinic variation showed that most of the improvement in mean glycaemic control occurred after 2008/9 while most of the reduction in the proportion of variance in HbA1c at the clinic level occurred before 2008. Over the last decade, there have been many changes in the landscape of paediatric diabetes. The drop in the national mean HbA1c levels occurred around the same time as the establishment of the regional Paediatric Diabetes Networks (PDN) in England in 2010, with most of the networks being already active for some years prior to this. The purpose of the PDN was to maintain high-quality standards of care in paediatric diabetes by coordinating care, promoting good practice, and drawing support from relevant stakeholders.

The 2012 NHS Diabetes Atlas of Variation was the first report to explicitly address the problem of regional variation in treatment targets for children with diabetes in England. Recognition of these variations led to the implementation of a number of different initiatives in paediatric diabetes care which might be relevant to the observed improvement in the national average glycaemic control. A Best Practice Tariff (BPT) for paediatric diabetes was introduced in April 2012 in England, enabling enhanced payments for clinics that meet specific criteria (125). Other important initiatives include the introduction of Patient Reported Experience Measures (PREM) since 2012/13 and the implementation of a two-year National peer review program for
meeting quality standards. Finally, public reporting of performance indicators became available in England and Wales in 2012/13, allowing each paediatric diabetes clinic to be openly identified through the publication of performance results in the public domain. Figure 30 below illustrates the key reports and initiatives in paediatric diabetes care in England and Wales between 2005 and 2015.

Another possible interpretation for the improvements observed in the mean HbA\textsubscript{1c} value might be the increasing use of more intensive methods of insulin therapy in England and Wales including the use of insulin pumps. NPDA reports have documented an increase in the use of insulin pumps from 16\% in 2013 to 23\% in 2014 (30). Since children on pumps have been shown to achieve better glycaemic control, it is possible that at least some of the improvements in national HbA\textsubscript{1c} levels are related to the increasing prevalence of pump use. However, the exact contribution of insulin pumps to the glycaemic improvement over the study period could not be formally tested since data on insulin pumps were not available before 2011.
Figure 30. Key reports and initiatives in paediatric diabetes care in England and Wales, 2005-2014.

The current study used robust statistical methods to analyse longitudinal data from a national cohort of over 40,000 children with T1D in England and Wales. Interpretation of the findings, however, should be done within the context of the study limitations. First, national coverage over the first three years of the study period was suboptimal with 51-59% of clinics contributing data to the NPDA. This low participation might have affected the variance estimates of these audit years. Results from the sensitivity analyses on clinics that participated over the whole study period showed a similar pattern of change in the share of HbA₁c variance at the clinic level. However, the magnitude of change was smaller. This suggests that low participation of clinics might have resulted in an overestimation of clinic variance. Second, there were inconsistencies in the way glycaemic data had been recorded across the study period (e.g. different number of recorded yearly HbA₁c measurements) which might have affected the results. For example, it is not known whether the one yearly HbA₁c
measurement recorded for each child during the first five years represented a random measurement, an average of all yearly measurements, or even the “best” measurement achieved during the audit year. Finally, the case-mix adjustment was limited to available data and did not include potentially important variables outside the control of the clinic such as parental education, family environment, comorbidities, and individual measures of socioeconomic status. However, a sensitivity analysis which adjusted for ethnicity and small-area deprivation yielded very similar results.
Chapter 9  Thesis conclusion

The main aim of the current thesis was to explore the impact of clinic context on glycaemic control of children and young people with T1D. Results of previous observational studies had consistently emphasised the existence of substantial differences between diabetes clinics but had failed to provide a clear answer as to how these differences fit into the total variability observed in children’s glycaemic outcomes and what aspects of diabetes services could adequately explain the observed clinic variations. To further explore these aspects, the current thesis analysed national data from England and Wales and other high-income countries in order to quantify variation between diabetes practices, understand the scope of narrowing clinic differences from a health policy perspective and also look, in more detail, into the role of input, structure, and process indicators related to paediatric diabetes care.

9.1  Overview of main findings

9.1.1  Variation in glycaemic control: between clinics and within clinics

Analysis of variation in HbA$_{1c}$ of children with T1D showed that two out of five clinics in England and Wales had a glycaemic performance which deviated significantly from the national average. However, these differences accounted for 4-5% of the total variation in glycaemic control, with variation within clinics being much more important. In fact, not only was most of the variation in HbA$_{1c}$ located within clinics, but children who attended clinics with less variable glycaemic performance had significantly better glycaemic control. However, detailed analysis of variation in HbA$_{1c}$ suggested that the impact of the clinic on children’s glycaemic control is not
the same for everyone, with younger children and children on pumps being more susceptible to the clinic environment.

9.1.2 Staffing levels and other service-related characteristics

Staffing levels varied considerably between the UK nations with significant gaps in the provision of 24/7 access to advice from the diabetes team. However, heavier staff caseloads in England and Wales were only weakly associated with poorer glycaemic control. Similarly, other clinic characteristics such as the size of the clinic, and the regional network where the clinic belongs, made a limited contribution to explaining children’s glycaemic outcomes. Finally, intensity of insulin regimen could not adequately explain the impact of clinic environment on children’s glycaemic outcomes.

9.1.3 Psychological services and psycho-educational programs

Provision of psychological support has improved over the last years with four out of five services in the UK having a dedicated psychologist as a member of the multidisciplinary team. Moreover, there was some indication that provision of psychological support was linked with better glycaemic control among ethnic minority children. Evidence from interventional studies showed that most of the psycho-educational programs in the UK were offered to adolescents and had a limited impact on diabetes outcomes, possibly because various NHS staff were trained to deliver the interventions rather than using dedicated psychologists.
9.1.4 Time trends and international comparison of variation in HbA₁c

National average glycaemic achievement of children and adolescents with T1D in England and Wales has shown significant improvements over the last decade, comparable to those observed in other similar European counties. The glycaemic improvement has been accompanied by a reduction in variation between clinics as a proportion of the total variation in HbA₁c. However, England and Wales continue to perform poorly when compared with other high-income countries such as Sweden, Denmark, and Norway. Finally, some of the best clinics in England and Wales performed poorly when compared even with some of the “worse” Swedish clinics.

9.2 Strengths and limitations

Strengths and limitations have been described separately in each chapter. Here, the overarching strengths and limitations of the whole thesis will be discussed.

The current thesis has contributed towards a better understanding of individual differences in glycaemic control of children with T1D and the role of clinic-level factors in explaining those differences. To the best of the author’s knowledge, this is the first study to use a robust multilevel analytical approach to quantify the impact of clinic context on glycaemic control of children with T1D. Multilevel (hierarchical) models accounted for random variation in clinic performance and allowed for the clustering of data within clinics. Another major strength of this work is the use of large national datasets from diabetes audits and registries with very high coverage, in most cases close to 100%. Such large datasets provided enough power to examine variations and also increased the external validity of the findings. Also, the use of international
data from high-income countries provided useful opportunities for cross-country learning.

A common limitation in the analyses of the current thesis was related to problems of routinely collected data (i.e. audit data), including misclassification, missing data, potential errors in data collection and entry, and limited number of available variables for case-mix adjustment. Adjusting children’s glycaemic control according to case-mix (i.e. differences in co-morbidity, personal attributes and environmental factors that are outside the control of the clinic) is important to ensure comparability between clinics and secure credibility with practitioners. The limited number of available case-mix variables means that causality bias cannot be completely eliminated and that attribution of observed clinic variations to differences in the quality of diabetes care should be made with caution. For example, access to additional case-mix variables such as co-morbidities, parental education, and individual socioeconomic status could be particularly useful.

9.3 Policy implications and recommendations

A number of key issues have been addressed in this thesis. The overarching policy implications arising from the findings are discussed below. Recommendations for future study are also provided.

9.3.1 Narrowing clinic differences is important but not sufficient

Reduction of clinic variations should always be a strategic goal of equitable healthcare systems, and choice of the clinic should play no role in determining a child’s glycaemic control. However, the current thesis showed that even if we are to eliminate all clinic
differences in England and Wales, we will manage to confer improvements in only a small proportion (~4-5%) of the total variation in HbA1c for children with T1D. It is unsurprising that clinic-level factors made only a limited contribution to explaining children’s glycaemic control even though, in some cases, they produced statistically significant results. Clinic variation was small relative to the total variability observed in HbA1c. So, even if we manage to explain a high proportion of clinic variation, we still end up explaining a small amount of the total variability in the outcome. A recent simulation study has found that the smaller the ICC is, the easier it is to find small but statistically significant contextual effects (159). This is precisely the case revealed in the current thesis.

Quality of diabetes care needs to be viewed through the lenses of a Continuous Quality Improvement model that seeks to improve quality of care in all clinics no matter how well they perform. Choosing to intervene only on outliers with poor performance is problematic for two main reasons. First, we would miss most children in need simply because they are heterogeneously distributed across all clinics, therefore, resulting in inefficient allocation of resources. Second, by removing the “bad apples” from the barrel, we are not addressing the quality problems that originate from competent practices in the middle range which are not performing optimally.

In terms of health policy, implementing interventions that primarily aim to reduce variations in paediatric diabetes care are unlikely to be sufficient in making nationwide improvements. For example, traditional peer review programs often adhere to the principle of “bad apples”, aiming to “discipline” services for non-compliance to minimum standards of care rather than to improve their quality through education.
9.3.2 Reducing variability within clinics

A considerable amount (i.e. \( \sim 85\% \)) of the total variability in children’s glycaemic control remained unexplained, even after adjusting for important case-mix and treatment characteristics including age, gender, duration of diabetes, ethnicity status, small-area deprivation, and insulin regimen. Of note, about 95\% of this unexplained variability in children’s glycaemic control was located within rather than between clinics. This means that if national improvements are to be made, England and Wales need to look more carefully at the extent of variability within clinics, understand its sources and develop strategies to reduce it.

It is expected that a significant component of the variability within clinics reflects variation between children in factors on which clinics have limited or no control. For example, children’s glycaemic control is heavily influenced by factors outside the health system. Such factors include the family environment and financial circumstances, parental education, dietary habits, and physical activity levels. Further quantitative and qualitative studies are needed to explore these sources of variability. Reducing variation in such factors will require changes in different levels and sectors such as education, employment, and taxation, where the product of health is not a primary goal.

Although part of the within clinic variability in children’s glycaemic control relates to individual factors that are outside the control of the clinics, it is possible that another component of the within clinic variability is attributable to variations between clinicians and healthcare professionals within the clinic. This portion of within clinic variability is within the control of the clinic and reflects the effectiveness of doctor-
patient consultation in influencing glycaemic outcomes of children with T1D. Evidence from analysis of patient experience measures in primary care has shown that the proportion of variance in experience scores due to differences between clinicians is considerably more than that due to practices (160). It has also been shown that aggregating measures at practice level can mask considerable variation in the performance of individual clinicians, particularly in lower performing practices (160). Future studies on T1D could further explore this component of variability by collecting data at the level of the clinician in addition to the level of the clinic. Such data could distinguish between clinicians and clinics contribution to differences in children’s outcomes.

9.3.3 “Shifting the curve” of all clinics towards better quality: lessons from Sweden and other Nordic counties

Results of the current thesis suggested that nationwide improvements in glycaemic control might best be achieved not only by narrowing clinic differences but also by focusing on the entire population of children with T1D regardless of the clinic they attend. This includes adopting a “whole system” approach that encourages changes in all clinics, even in some of the best performing clinics of the country.

This raises the question of which policies have the potential to facilitate this “whole system” approach to quality improvement. The recent change in NICE guidelines towards tighter glycaemic targets for children with diabetes in the UK might help towards this direction. However, this change is unlikely to be sufficient, by itself, in bringing about such improvements. Patient-centred policies have been shown to be useful in stimulating whole system improvements. The recent introduction of patient
reported experience measures (PREM) in paediatric diabetes care in England and Wales in 2012 is an important initiative which could help providers across the country identify aspects of diabetes care with the greatest potential to influence glycaemic outcomes.

England and Wales can also learn useful lessons from Sweden and other Nordic countries which have long established a national program of continuous quality improvement adopting a “whole system” approach in paediatric diabetes care that might be relevant to their success in achieving homogeneously good glycaemic results.

In Nordic countries, the development of a national quality register in paediatric diabetes care has been a key driver of quality improvements. Quality registers provide clinicians and members of the diabetes team with information on several quality indicators with which to monitor performance between clinics and over time and also facilitate discussions on improvement (135). In this respect, quality registers in Nordic countries share many common features with the national audit in England and Wales. However, there are noteworthy differences. For example, data from Sweden’s quality register are used not only as a means of assessment and scrutiny but also as a clinical tool to support local decision-making and assist professional development through continuous learning and collaboration with other members of the register. In other words, measurement of quality indicators is inextricably linked with a clinician’s lifelong learning. This link between performance measurement and professional development might be key to Sweden’s success.

The active participation of Swedish centres in quality improvement collaboratives is another example of the “whole system” approach in paediatric diabetes care.
Collaboratives focus on education and systematic improvement and include learning sessions during which teams from different clinics meet and discuss the application of quality improvement initiatives within their institutions in such topics as reducing waiting times, improving diabetes education, and teamwork. Following the Swedish example, the RCPCH has recently piloted a similar Quality Improvement Collaborative at both regional and national level which is expected to start in 2018.

Cross-country comparisons in diabetes care need also to be interpreted in the light of broader policies including markers of health prioritisation and spending (e.g. percentage of Gross Domestic Product spent on healthcare) as well as policies in areas where the product of health is not a primary goal, such as employment, education, and housing. For example, countries like Sweden and Norway are widely perceived as homogeneous countries which share a comparable approach to social welfare and place an increased emphasis on reducing the gap between rich and poor (156). These differences might be relevant to the observed variations in HbA1c levels.

9.4 Concluding remarks

Quality of paediatric diabetes care in England and Wales is monitored through a range of mechanisms; these include the NICE guidelines, the Best Practice Tariff, the National Children and Young People's Diabetes Network, the Peer Review programme, and the National Paediatric Diabetes Audit. Such quality assurance mechanisms increasingly reflect the patient pathway but more could be done to ensure they are understood and oriented towards patients and clinicians.

Diabetes care for children in England and Wales needs to move beyond a tick-box culture of inspecting compliance against minimum standards to a more meaningful
assessment of the quality of care that focuses on bottom-up approaches led by patients and clinicians and encourages changes in all clinics regardless of their performance. The move to a Continuous Quality Improvement model of care for diabetes requires a more systematic collection of individual-level data to measure performance, particularly on patient experience measures. England and Wales do well on this. The challenge is to make sure that collecting these measures reflects patient’s active rather than passive involvement and also that such data are used effectively to inform clinicians’ professional development and local practice.
Bibliography


Appendix A: Confirmation of ethical exemption

Dr Dimitros Charalampopoulos
Research Associate
4th floor, Open Plan
Children’s Policy Research Unit (CPRU),
UCL Institute of Child Health
30 Guilford Street
London
WC1N 1EH

11 July 2014

Dear Dr Charalampopoulos

Confirmation of Ethical Exemption

In my capacity as Chair of the UCL Research Ethics Committee, I have reviewed your project which aims to use data from the National Paediatric diabetes Audit (NPDA) to explore variation in diabetes care processes and outcome and can confirm that your study falls within the definition of an ‘Audit’ as defined below and is therefore exempt from the requirement to obtain ethical approval.

Audit is defined as assessing the level of service being provided against a set of pre-determined standards. This generally involves analysing existing data with results usually being used/distributed locally in order to effect change to improve or change the level of service currently being provided.

Yours sincerely

Professor John Foreman
Chair, UCL Research Ethics Committee
Cc: Professor Terence Stephenson, Project Supervisor, UCL Institute of Child Health
Appendix B: Detailed results of complex variance multilevel models in Chapter 4
Table 1. Multilevel models with children at level 1 and clinics at level 2. Subscript 1 for 0-4 years, 2 for 5-9 years, 3 for 10-14 years, 4 for 15-18 years, 5 for continuous age (mean-centred)

<table>
<thead>
<tr>
<th>Random intercept, case-mix adjusted model</th>
<th>Model 1 Age categorical random at level 1</th>
<th>Model 3 Age categorical random at both levels</th>
<th>Model 3 Age categorical random at both levels</th>
<th>Model 4 Age centred continuous random at level 1</th>
<th>Model 5 Age continuous random at both levels</th>
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Note: Models 3 (age categorical) and 5 (age continuous) were selected a best fitting models. VPC= variance partitioning coefficient.
Table 2. Multilevel models with children at level 1 and clinics at level 2. Subscript 5 for boys, and 6 for girls

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Note: Model 1 selected as the best fitting model. VPC= variance partitioning coefficient.
Table 3. Multilevel models with children at level 1 and clinics at level 2. Subscript 7 for duration <2 years, 8 for duration ≥2 years

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</table>

Note: Model 2 selected as the best fitting model. VPC= variance partitioning coefficient.
Table 4. Multilevel models with children at level 1 and clinics at level 2. Subscript 9 for deprivation quintile 1, 10 for quintile 2, 11 for quintile 3, 12 for quintile 4, 13 for quintile 5, 14 for deprivation quintiles entered as a continuous variable (centered)

<table>
<thead>
<tr>
<th>Random effects</th>
<th>Random intercept model Case-mix adjusted</th>
<th>Model 1 Deprivation categories random at level 1</th>
<th>Model 2 Deprivation categories random at both levels</th>
<th>Model 3 Deprivation categories random at both levels</th>
<th>Model 4 Continuous Deprivation random at level 1</th>
<th>Model 5 continuous Deprivation random at both levels</th>
<th>Model 6 continuous Deprivation random at both levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td></td>
</tr>
<tr>
<td>$\sigma^2_{u0}$</td>
<td>12.412 (1.584)</td>
<td>12.160 (1.553)</td>
<td>12.029 (1.551)</td>
<td>12.176 (1.556)</td>
<td>12.213 (1.571)</td>
<td>12.161 (1.565)</td>
<td></td>
</tr>
<tr>
<td>$\sigma_{u010}$</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma_{u011}$</td>
<td>0.167 (1.073)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma_{u012}$</td>
<td>0.000 (0.000)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma_{u013}$</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma_{u014}$</td>
<td>1.881 (1.605)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma_{u101}$</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>$\sigma_{u102}$</td>
<td>0</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>$\sigma_{u103}$</td>
<td>0</td>
<td></td>
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<tr>
<td>$\sigma_{u112}$</td>
<td>0</td>
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<tr>
<td>$\sigma_{u113}$</td>
<td>0</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>$\sigma_{u123}$</td>
<td>1.285 (1.468)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma_{u014}$</td>
<td>0.674 (0.354)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma_{u014}$</td>
<td>0.263 (0.146)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma^2_{e0}$</td>
<td>249.508 (2.401)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma^2_{e0}$</td>
<td>201.079 (4.335)</td>
<td>200.989 (4.334)</td>
<td>200.740 (4.336)</td>
<td>252.974 (3.755)</td>
<td>252.799 (3.753)</td>
<td>252.862 (3.753)</td>
<td></td>
</tr>
<tr>
<td>$\sigma^2_{e1}$</td>
<td>223.199 (4.815)</td>
<td>223.013 (4.855)</td>
<td>223.220 (4.858)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma^2_{e2}$</td>
<td>256.659 (5.534)</td>
<td>256.626 (5.535)</td>
<td>256.411 (5.541)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma^2_{e3}$</td>
<td>275.719 (5.945)</td>
<td>275.728 (5.947)</td>
<td>275.942 (6.011)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma^2_{e4}$</td>
<td>291.56 (6.275)</td>
<td>290.161 (6.302)</td>
<td>290.192 (6.301)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>$\sigma^2_{e5}$</td>
<td>-1.700 (1.424)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>$\sigma^2_{e6}$</td>
<td>-1.837 (1.424)</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma^2_{e7}$</td>
<td>-1.861 (1.424)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>$\sigma^2_{e8}$</td>
<td>11.639 (0.855)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma^2_{e9}$</td>
<td>11.534 (0.854)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma^2_{e10}$</td>
<td>11.599 (0.854)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>$\sigma^2_{e11}$</td>
<td>182.295</td>
<td>182.100</td>
<td>182.098</td>
<td>182.088</td>
<td>182.101</td>
<td>182.093</td>
<td>182.097</td>
</tr>
<tr>
<td>VPC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All children (ICC)</td>
<td>4.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deprivation quintile 1</td>
<td>5.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deprivation quintile 2</td>
<td>4.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deprivation quintile 3</td>
<td>4.6%</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Table 5. Multilevel models with children at level 1 and clinics at level 2. Subscript 15 for white, 20 for non-white

<table>
<thead>
<tr>
<th></th>
<th>Random intercept case-mix adjusted model</th>
<th>Model 1 binary ethnicity random at level 1</th>
<th>Model 2 binary ethnicity random at both levels</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Random effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Level 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma^2_{y0}$</td>
<td>12.412 (1.584)</td>
<td>12.304 (1.571)</td>
<td>12.151 (1.563)</td>
</tr>
<tr>
<td>$\sigma_{u020}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma^2_{u20}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Level 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma^2_{e15}$</td>
<td>249.508 (2.401)</td>
<td>243.064 (2.478)</td>
<td>243026 (2.478)</td>
</tr>
<tr>
<td>$\sigma^2_{e20}$</td>
<td></td>
<td>302.391 (8.827)</td>
<td>300.530 (8.871)</td>
</tr>
<tr>
<td><strong>-2 L.L.</strong></td>
<td>182,295</td>
<td>182,243</td>
<td>182,241</td>
</tr>
<tr>
<td><strong>VPC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All children (ICC)</td>
<td>4.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td></td>
<td>4.8%</td>
<td></td>
</tr>
<tr>
<td>Non-white</td>
<td></td>
<td>3.9%</td>
<td></td>
</tr>
</tbody>
</table>

Note: Model 1 selected as the best fitting model. VPC = variance partitioning coefficient.
Table 6. Multilevel models with children at level 1 and clinics at level 2. Subscript 2 for injection users, and 3 for insulin pump users

<table>
<thead>
<tr>
<th></th>
<th>Random intercept, case-mix adjusted model</th>
<th>Insulin regimen random at both levels</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Random effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma^2_{u0}$</td>
<td>12.412 (1.584)</td>
<td>12.44 (1.75)</td>
</tr>
<tr>
<td>$\sigma_{u03}$</td>
<td>-3.08 (1.51)</td>
<td></td>
</tr>
<tr>
<td>$\sigma^2_{u3}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma^2_{e0}$</td>
<td>249.508 (2.401)</td>
<td>258.11 (2.94)</td>
</tr>
<tr>
<td>$\sigma^2_{e2}$</td>
<td></td>
<td>154.85 (3.92)</td>
</tr>
<tr>
<td>$\sigma^2_{e3}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>-2 LL</strong></td>
<td>182.295</td>
<td>-</td>
</tr>
<tr>
<td><strong>VPC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All children (ICC)</td>
<td>4.7%</td>
<td></td>
</tr>
<tr>
<td>Injection users</td>
<td>4.2%</td>
<td></td>
</tr>
<tr>
<td>Pump users</td>
<td>8.5%</td>
<td></td>
</tr>
</tbody>
</table>

Note: Data for insulin regimen were missing for 2,933 children (13.5%) and were imputed using multiple imputation.

VPC= variance partitioning coefficient.
Appendix C: Detailed results of multilevel models in Chapter 5
### Two-level models with a random effect for clinic. SE=standard error

<table>
<thead>
<tr>
<th>Components of variance</th>
<th>Variance (SE)</th>
<th>Variance (SE)</th>
<th>Variance (SE)</th>
<th>Variance (SE)</th>
<th>Variance (SE)</th>
<th>Variance (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between clinics</td>
<td>16.4 (2.1)</td>
<td>12.4 (1.6)</td>
<td>11.8 (1.5)</td>
<td>11.0 (1.4)</td>
<td>11.9 (1.5)</td>
<td>6.0 (0.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.6 (0.9)</td>
</tr>
<tr>
<td>Between individuals</td>
<td>287.6 (2.9)</td>
<td>249.5 (2.4)</td>
<td>246.6 (2.4)</td>
<td>249.5 (2.4)</td>
<td>249.5 (2.4)</td>
<td>249.5 (2.4)</td>
</tr>
</tbody>
</table>

### Fixed effects

<table>
<thead>
<tr>
<th>Unadjusted</th>
<th>Case-mix adjusted + individual regimen</th>
<th>Case-mix adjusted + regional networks</th>
<th>Case-mix adjusted + clinic volume</th>
<th>Case-mix adjusted + clinic HbA1c-SD</th>
<th>Case-mixed adjusted + clinic volume + clinic HbA1c-SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>coefficients (95% CI)</td>
<td>coefficients (95% CI)</td>
<td>coefficients (95% CI)</td>
<td>coefficients (95% CI)</td>
<td>coefficients (95% CI)</td>
</tr>
<tr>
<td>Age (mean centered years)</td>
<td>-0.1 (0.2 to 0.004)</td>
<td>-0.2 (0.3 to 0.04)</td>
<td>-0.1 (0.2 to 0.003)</td>
<td>-0.1 (0.2 to 0.003)</td>
<td>-0.1 (0.2 to 0.003)</td>
</tr>
<tr>
<td>Female (reference: male)</td>
<td>1.3 (0.9 to 1.7)</td>
<td>1.4 (1.0 to 1.8)</td>
<td>1.3 (0.9 to 1.7)</td>
<td>1.3 (0.9 to 1.7)</td>
<td>1.3 (0.9 to 1.7)</td>
</tr>
</tbody>
</table>

### Duration of diabetes (reference: <1 year)

<table>
<thead>
<tr>
<th>Age category</th>
<th>Unadjusted</th>
<th>Case-mix adjusted + individual regimen</th>
<th>Case-mix adjusted + regional networks</th>
<th>Case-mix adjusted + clinic volume</th>
<th>Case-mix adjusted + clinic HbA1c-SD</th>
<th>Case-mixed adjusted + clinic volume + clinic HbA1c-SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>coefficients (95% CI)</td>
<td>coefficients (95% CI)</td>
<td>coefficients (95% CI)</td>
<td>coefficients (95% CI)</td>
<td>coefficients (95% CI)</td>
<td>coefficients (95% CI)</td>
</tr>
<tr>
<td>1-2 years</td>
<td>7.3 (6.4 to 8.1)</td>
<td>7.5 (6.6 to 8.4)</td>
<td>7.3 (6.4 to 8.2)</td>
<td>7.2 (6.3 to 8.1)</td>
<td>7.2 (6.3 to 8.1)</td>
<td>7.2 (6.3 to 8.1)</td>
</tr>
<tr>
<td>2-5 years</td>
<td>9.7 (9.0 to 10.4)</td>
<td>10.2 (9.5 to 10.9)</td>
<td>9.7 (9.0 to 10.4)</td>
<td>9.7 (9.0 to 10.4)</td>
<td>9.7 (9.0 to 10.4)</td>
<td>9.7 (9.0 to 10.4)</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>10.7 (10.0 to 11.4)</td>
<td>11.4 (10.7 to 12.1)</td>
<td>10.7 (10.0 to 11.4)</td>
<td>10.7 (10.0 to 11.4)</td>
<td>10.7 (10.0 to 11.4)</td>
<td>10.7 (10.0 to 11.4)</td>
</tr>
</tbody>
</table>

### Interaction of age with duration

<table>
<thead>
<tr>
<th>Age*duration</th>
<th>Unadjusted</th>
<th>Case-mix adjusted + individual regimen</th>
<th>Case-mix adjusted + regional networks</th>
<th>Case-mix adjusted + clinic volume</th>
<th>Case-mix adjusted + clinic HbA1c-SD</th>
<th>Case-mixed adjusted + clinic volume + clinic HbA1c-SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>coefficients (95% CI)</td>
<td>coefficients (95% CI)</td>
<td>coefficients (95% CI)</td>
<td>coefficients (95% CI)</td>
<td>coefficients (95% CI)</td>
<td>coefficients (95% CI)</td>
</tr>
<tr>
<td>2nd</td>
<td>0.8 (0.6 to 1.0)</td>
<td>0.8 (0.6 to 1.0)</td>
<td>0.8 (0.6 to 1.0)</td>
<td>0.8 (0.6 to 1.0)</td>
<td>0.8 (0.6 to 1.0)</td>
<td>0.8 (0.6 to 1.0)</td>
</tr>
<tr>
<td>3rd</td>
<td>1.3 (1.1 to 1.5)</td>
<td>1.3 (1.1 to 1.4)</td>
<td>1.3 (1.1 to 1.5)</td>
<td>1.3 (1.1 to 1.5)</td>
<td>1.3 (1.1 to 1.5)</td>
<td>1.3 (1.1 to 1.5)</td>
</tr>
<tr>
<td>4th</td>
<td>1.5 (1.3 to 1.6)</td>
<td>1.4 (1.3 to 1.6)</td>
<td>1.5 (1.3 to 1.6)</td>
<td>1.5 (1.3 to 1.6)</td>
<td>1.5 (1.3 to 1.6)</td>
<td>1.5 (1.3 to 1.6)</td>
</tr>
</tbody>
</table>

### Ethnicity (reference: White)

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Unadjusted</th>
<th>Case-mix adjusted + individual regimen</th>
<th>Case-mix adjusted + regional networks</th>
<th>Case-mix adjusted + clinic volume</th>
<th>Case-mix adjusted + clinic HbA1c-SD</th>
<th>Case-mixed adjusted + clinic volume + clinic HbA1c-SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>6.6 (4.9 to 8.2)</td>
<td>6.1 (4.4 to 7.7)</td>
<td>6.4 (4.8 to 8.1)</td>
<td>6.5 (4.9 to 8.2)</td>
<td>6.2 (4.6 to 7.8)</td>
<td>6.2 (4.5 to 7.8)</td>
</tr>
<tr>
<td>Mixed</td>
<td>4.8 (3.5 to 6.2)</td>
<td>4.7 (3.4 to 6.0)</td>
<td>4.7 (3.4 to 6.1)</td>
<td>4.8 (3.5 to 6.2)</td>
<td>4.6 (3.3 to 6.0)</td>
<td>4.6 (3.3 to 6.0)</td>
</tr>
<tr>
<td>Other</td>
<td>1.8 (0.1 to 3.6)</td>
<td>1.6 (0.2 to 3.5)</td>
<td>1.7 (0.2 to 3.5)</td>
<td>1.8 (0.1 to 3.6)</td>
<td>1.5 (0.3 to 3.4)</td>
<td>1.5 (0.3 to 3.4)</td>
</tr>
<tr>
<td>Not reported</td>
<td>-0.4 (-1.3 to 0.5)</td>
<td>-0.5 (-1.4 to 0.4)</td>
<td>-0.4 (-1.3 to 0.4)</td>
<td>-0.4 (-1.3 to 0.5)</td>
<td>-0.3 (-1.1 to 0.6)</td>
<td>-0.2 (-1.1 to 0.6)</td>
</tr>
</tbody>
</table>

### Treatment (reference: <4 insulin injections/day)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Unadjusted</th>
<th>Case-mix adjusted + individual regimen</th>
<th>Case-mix adjusted + regional networks</th>
<th>Case-mix adjusted + clinic volume</th>
<th>Case-mix adjusted + clinic HbA1c-SD</th>
<th>Case-mixed adjusted + clinic volume + clinic HbA1c-SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤3 insulin injections/day</td>
<td>1.5 (0.8 to 2.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin Pump Therapy</td>
<td>-4.7 (-3.3 to -4.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Clinic-level characteristics

<table>
<thead>
<tr>
<th>Diabetes Networks (reference: East of England)</th>
<th>Unadjusted</th>
<th>Case-mix adjusted + individual regimen</th>
<th>Case-mix adjusted + regional networks</th>
<th>Case-mix adjusted + clinic volume</th>
<th>Case-mix adjusted + clinic HbA1c-SD</th>
<th>Case-mixed adjusted + clinic volume + clinic HbA1c-SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>East Midlands</td>
<td>-4.5 (-7.4 to -1.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North East</td>
<td>-3.0 (-6.0 to 0.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>London</td>
<td>-1.1 (-3.6 to 1.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North West</td>
<td>-2.6 (-5.0 to -0.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South East</td>
<td>-1.8 (-4.1 to 0.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South West</td>
<td>-2.2 (-4.9 to 0.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Central</td>
<td>-3.9 (-6.5 to -1.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wales</td>
<td>-2.4 (-5.1 to 0.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>West Midlands</td>
<td>-1.3 (-3.3 to 1.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinic size (per 100 children)</th>
<th>Unadjusted</th>
<th>Case-mix adjusted + individual regimen</th>
<th>Case-mix adjusted + regional networks</th>
<th>Case-mix adjusted + clinic volume</th>
<th>Case-mix adjusted + clinic HbA1c-SD</th>
<th>Case-mixed adjusted + clinic volume + clinic HbA1c-SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-1.0 (-1.9 to -0.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c SD (per 10 mmol/mol decrease)</td>
<td>-10.0 (-11.6 to -8.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Two-level models with a random effect for clinic. SE=standard error

Estimates are based on imputed data.
Appendix D: Narrative description of data sources

Prospective Diabetes Follow-up Registry (DPV)

Diabetes Prospective Follow-up (DPV) registry in Germany and Austria represents a large consortia of diabetes centres that were established with an objective of improving diabetes care through sharing of best practices and the collection of clinical outcome data in large numbers of patients. The DPV registry is a prospective longitudinal, standardised, and computer-based documentation system for patients (children and adults) with all types of diabetes. Twice yearly, anonymised data are exported by diabetes centres and transmitted for central analyses. Missing and inconsistent data are reported back to the centres for correction. DPV covers 90% of all paediatric patients with diabetes in Germany and 80% of all paediatric patients with diabetes in Austria. Data collection is approved by the ethics committee at Ulm University and by the IRBs at the participating centres. The German BMBF Competence Net Diabetes Mellitus (FKZ 01GI1106), which is integrated into the German Centre for Diabetes Research (DZD) as of January 2015, and the European Foundation for the Study of Diabetes (EFSD) support funding of DPV.

Danish National Diabetes Registry (DanDiabKids)

The Danish database is a National Quality Register – meaning that all have to send a HbA1c for central measure for each child they follow in the clinic and they have to give input to the database annually concerning hypoglycaemia, ketoacidosis treatment etc. The database is approved by the authority with the number: KA 95139M.
Norwegian Childhood Diabetes Registry (NCDR)

NCDR is funded by the Department of Health and is managed by the South-Eastern Norway Regional Health Authority and Oslo University Hospital. In the Norwegian health care system, all children aged 0-14.9 years with suspected diabetes are referred to a paediatric department. The NCDR includes all new cases of childhood-onset diabetes, reported from all the paediatric departments in Norway, based on informed consent from the child and/or their parents. Cases are included as type 1 diabetes in the NCDR based on a clinical diagnosis of type 1 diabetes, using the first insulin injection as the date of diagnosis, in accordance with the EURODIAB criteria. The Clinical Practice Consensus Guidelines published by the International Society of Paediatric and Adolescent Diabetes (ISPAD) has been implemented. NCDR has a standardised registration at the onset of diabetes and at follow-up, conducted at the local paediatric departments. All the paediatric departments are collecting data. The data is then reported to NCDR. Data for this study were collected between 1 January 2013 and 31 December 2013.

Swedish Paediatric Diabetes Quality Registry (SWEDIABKIDS)

SWEDIABKIDS is financially supported by the Association of Local Authorities and Regions, SALAR, which represents the interests of Sweden’s municipalities, county councils, and regions. SWEDIABKIDS has the status of a national quality registry. The quality registry SWEDIABKIDS was established in 2000 and includes outpatient ambulatory data from all Swedish paediatric diabetes centres (n=42). Since 2008, the registry has been available online to all paediatric diabetes centres in Sweden. All children and adolescents aged 0 to 18 years with diabetes are treated at specialised
paediatric centres in Sweden, and the registry includes data on almost all (around 98%) of the children and adolescents with diabetes in Sweden. Data is documented in the registry at every visit to the clinic. The results are presented online, openly naming the centres, and can be accessed by the public (https://swediabkids.ndr.nu/). SWEDIABKIDS allows each team to online continuously follow its quality indicators and results, and to benchmark its results with other teams as well as with the national results.

T1D Exchange

The T1D Exchange Clinic Network includes over 80 US-based paediatric and adult endocrinology practices in 34 states. A registry of more than 26,000 individuals with T1D commenced enrolment in September 2010. Each clinic received approval from a local institutional review board (IRB). Informed consent was obtained according to IRB requirements. Data were collected for the registry's central database from the participant's medical record and by having the participant or parent complete a comprehensive questionnaire.
Appendix E: Mathematical notations of multilevel model

A three-level hierarchical regression model was used to analyse variation in HbA1c (hba1cmol), with HbA1c measurement occasions at level 1 (i), individual children as level 2 (j), and diabetes clinics at level 3 (k). Under the specified model, HbA1c values are normally distributed with the mean given by the fixed part of the model XB, where X denotes the set of explanatory variables and B their coefficients.

\[ \text{hba1cmol}_{ijk} \sim N(XB, \Omega) \]

The variance is \( \Omega \), which has a between clinic component (\( \Omega_v \)), a between individual component (\( \Omega_u \)), and a within individual component (\( \Omega_e \)). \( \Omega_v \) and \( \Omega_u \) are denoted by the matrices shown below. \( \Omega_e \) is denoted by the single value \( \sigma_{eo}^2 \).

\[
\begin{bmatrix}
  v_{0c} \\
  v_{1kc}
\end{bmatrix}
\sim N(0, \Omega_v) : \Omega_v = \begin{bmatrix}
  \sigma_{v0}^2 \\
  \sigma_{v1}^2 \\
  \sigma_{v13}^2 \\
  \sigma_{v14}^2 \\
  \sigma_{v13}^2 \\
  \sigma_{v14}^2
\end{bmatrix}
\]

\[
\begin{bmatrix}
  u_{jk} \\
  u_{1jk}
\end{bmatrix}
\sim N(0, \Omega_u) : \Omega_u = \begin{bmatrix}
  \sigma_{u0}^2 \\
  \sigma_{u1}^2 \\
  \sigma_{u13}^2 \\
  \sigma_{u14}^2 \\
  \sigma_{u13}^2 \\
  \sigma_{u14}^2
\end{bmatrix}
\]

\[
\begin{bmatrix}
  e_{ijk}
\end{bmatrix}
\sim N(0, \Omega_e) : \Omega_e = \sigma_{eo}^2
\]

The HbA1c value of an \( i \) th measurement from an \( j \) th individual who attends a clinic \( k \) is given as follows:

\[
\text{hba1cmol}_{ijk} = \beta_{0ijk}\text{cons} + \beta_{j\text{female}j} + \beta_{j\text{age}13j} + \beta_{j\text{age}12_2j} + \beta_{j\text{diagnecat}4_3j} + \beta_{j\text{diagnecat}4_4j} + \beta_{j\text{agediagage}1j} + \beta_{j\text{agediagage}2j} + \beta_{j\text{agediagage}3j} + \beta_{j\text{age2diagage}1j} + \beta_{j\text{age2diagage}2j} + \beta_{j\text{age2diagage}3j} + \beta_{j\text{age2diagage2}j} + \beta_{j\text{age2diagage3}j} + \beta_{j\text{audit_cen}1j} + \beta_{j\text{audit_cen}2j} + \beta_{j\text{audit_cen3}j}
\]
The following explanatory variables were added: gender (female), children’s age centered around its mean (age13), age\(^2\) (age13\_2), age at diagnosis categories [age at diagnosis \(<5\) yrs (reference); age at diagnosis 5-\(<10\) yrs (diagagecat4\_2); age at diagnosis 10-\(<15\) yrs (diagagecat4\_3); age at diagnosis \(\geq15\) yrs (diagagecat4\_4)], interaction terms between age, age\(^2\), and age at diagnosis categories [Age\(\times\) diagnosis age 5-\(<10\) yrs (agediagage1); Age\(\times\) diagnosis age 10-\(<15\) yrs (agediagage2); Age\(\times\) diagnosis age \(\geq15\) yrs (agediagage3); Age\(^2\)\(\times\) diagnosis age 5-\(<10\) yrs (age2diagage1); Age\(^2\)\(\times\) diagnosis age 10-\(<15\) yrs (age2diagage2); Age\(^2\)\(\times\) diagnosis age \(\geq15\) yrs (age2diagage3)], audit year centered around year 2009 (audit\_cen\(^1\)), audit year\(^2\) (audit\_cen\(^2\)), and audit year\(^3\) (audit\_cen\(^3\)).

Age and audit year were time-varying variables while gender and age at diagnosis were time-invariant variables.

\textit{Cons} was automatically added to the worksheet and its coefficient \(\beta_{0ijk}\) is the intercept.

The subscripts \(i\), \(j\), and \(k\) are added to the coefficients of any variable on which the within individual, between individual, and between clinic variances depend as shown below. The level 1 variance (within individual) is constant.

\[
\beta_{0ijk} = \beta_0 + v_{0k} + u_{0jk} + e_{0ijk}
\]

\[
\beta_{13jk} = \beta_{13} + v_{13k} + u_{13jk}
\]

\[
\beta_{14jk} = \beta_{14} + v_{14k} + u_{14jk}
\]

Between clinic variance as a function of audit year was calculated using the formula:

\[
\text{var}(v_{0k}\text{cons} + v_{13k}\text{audit\_cen}^1 \_1\_pk + v_{14k}\text{audit\_cen}^2 \_2\_pk) = \sigma_v^2\text{cons}^2 + 2\sigma_v\sigma_u\text{cons}^*\text{audit\_cen}^1 \_1\_pk + \sigma_u^2 \text{audit\_cen}^1 \_1\_pk^2 + 2\sigma_{v,13}\text{cons}^*\text{audit\_cen}^1 \_1\_pk \cdot \text{audit\_cen}^2 \_2\_pk + 2\sigma_{v,13}\text{audit\_cen}^1 \_1\_pk \cdot \text{audit\_cen}^2 \_2\_pk
\]

Between individual variance as a function of audit year was calculated using the formula:

\[
\text{var}(u_{0k}\text{cons} + u_{13k}\text{audit\_cen}^1 \_1\_pk + u_{14k}\text{audit\_cen}^2 \_2\_pk) = \sigma_u^2\text{cons}^2 + 2\sigma_u\sigma_v\text{cons}^*\text{audit\_cen}^1 \_1\_pk + \sigma_v^2 \text{audit\_cen}^1 \_1\_pk^2 + 2\sigma_{u,13}\text{cons}^*\text{audit\_cen}^1 \_1\_pk \cdot \text{audit\_cen}^2 \_2\_pk + 2\sigma_{u,13}\text{audit\_cen}^1 \_1\_pk \cdot \text{audit\_cen}^2 \_2\_pk
\]

\[
+ \sigma_{u,13}\text{audit\_cen}^2 \_2\_pk^2
\]
Within individual variance was constant.

\[ \text{var}(e_{\text{apc cons}}) = \sigma^2_{\text{apc cons}} \]

Total variance in HbA1c was calculated as the sum of between-clinic, between-individual, and within individual variances.

Variance Partitioning Coefficient (VPC) was calculated as the proportion of total variance at the level of the clinic:

\[ \text{VPC} (%) = \frac{\text{between-clinic variance}}{\text{total variance}} \times 100 \]

Since between-clinic and between-individual variances were a function of audit year, VPC is also a function of audit year.
### Appendix F: Chapter 8 sensitivity analysis 1

Results of 3-level hierarchical model analysing time trends in HbA1c levels in children<19 years with type 1 diabetes in England and Wales from 2005 to 2014 in a subsample of the national cohort with available data on ethnicity and deprivation (n=37,684)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard error</th>
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<tbody>
<tr>
<td>Constant</td>
<td>70.2</td>
<td>0.36</td>
</tr>
<tr>
<td>Year</td>
<td>-0.72</td>
<td>0.06</td>
</tr>
<tr>
<td>Year&lt;sup&gt;2&lt;/sup&gt;</td>
<td>-0.10</td>
<td>0.007</td>
</tr>
<tr>
<td>Year&lt;sup&gt;3&lt;/sup&gt;</td>
<td>0.009</td>
<td>0.002</td>
</tr>
<tr>
<td>Female</td>
<td>1.52</td>
<td>0.15</td>
</tr>
<tr>
<td>Age</td>
<td>1.48</td>
<td>0.04</td>
</tr>
<tr>
<td>Age&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.07</td>
<td>0.005</td>
</tr>
<tr>
<td>Age at diagnosis &lt;5 yrs (reference)</td>
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<tr>
<td>5-10 yrs</td>
<td>0.70</td>
<td>0.23</td>
</tr>
<tr>
<td>10-15 yrs</td>
<td>-6.12</td>
<td>0.24</td>
</tr>
<tr>
<td>15 yrs</td>
<td>-41.12</td>
<td>4.51</td>
</tr>
<tr>
<td>Age× diagnosis age 5-&lt;10 yrs</td>
<td>0.31</td>
<td>0.05</td>
</tr>
<tr>
<td>Age× diagnosis age 10-&lt;15 yrs</td>
<td>2.21</td>
<td>0.09</td>
</tr>
<tr>
<td>Age× diagnosis age ≥15 yrs</td>
<td>10.16</td>
<td>2.24</td>
</tr>
<tr>
<td>Age&lt;sup&gt;2&lt;/sup&gt;× diagnosis age 5-&lt;10 yrs</td>
<td>-0.12</td>
<td>0.009</td>
</tr>
<tr>
<td>Age&lt;sup&gt;2&lt;/sup&gt;× diagnosis age 10-&lt;15 yrs</td>
<td>-0.28</td>
<td>0.02</td>
</tr>
<tr>
<td>Age&lt;sup&gt;2&lt;/sup&gt;× diagnosis age ≥15 yrs</td>
<td>-0.74</td>
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</tr>
<tr>
<td>Ethnicity (white reference)</td>
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<tr>
<td>Non-white</td>
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<tr>
<td>Deprivation quintile (centered)</td>
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<td>0.06</td>
</tr>
<tr>
<td>Between-clinic variances/covariances</td>
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</tr>
<tr>
<td>Intercept variance</td>
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<td>1.41</td>
</tr>
<tr>
<td>Year variance</td>
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<td>0.11</td>
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<tr>
<td>Year&lt;sup&gt;2&lt;/sup&gt; variance</td>
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<td>0.004</td>
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<td>Intercept-year covariance</td>
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<td>0.28</td>
</tr>
<tr>
<td>Intercept-year&lt;sup&gt;2&lt;/sup&gt; covariance</td>
<td>-0.18</td>
<td>0.05</td>
</tr>
<tr>
<td>Year-year&lt;sup&gt;2&lt;/sup&gt; covariance</td>
<td>-0.10</td>
<td>0.02</td>
</tr>
<tr>
<td>Between-individual variances/covariances</td>
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<tr>
<td>Intercept variance</td>
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<td>2.27</td>
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<td>Year variance</td>
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<td>Year-year&lt;sup&gt;2&lt;/sup&gt; covariance</td>
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<td>0.02</td>
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<td>Within-individual variance</td>
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<td>-2Log-likelihood</td>
<td>1140948</td>
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Note: All continuous variables were centred on their mean.
Appendix G: Chapter 8 sensitivity analysis 2

Figure showing population average case-mix adjusted HbA1c values by audit year comparing results from the complete cohort (63 clinics which participated throughout the 10-year period) vs. the national cohort including all centres.
Figure showing the proportion of total variation at the level of the clinic by audit year comparing results from the complete cohort (63 clinics which participated throughout the 10-year period) vs. the national cohort including all centres.
Psycho-educational interventions for children and young people with Type 1 Diabetes in the UK: How effective are they? A systematic review and meta-analysis


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Abstract

Aims
To synthesise evidence from UK-based randomised trials of psycho-educational interventions in children and young people (CYP) with Type 1 Diabetes (T1D) to inform the evidence-base for adoption of such interventions into the NHS.

Methods
We searched Medline, Embase, Cochrane, PsycINFO, CINAHL, and Web of Science up to March 2016. Two reviewers independently selected UK-based randomised trials comparing psycho-educational interventions for improving management of T1D for CYP with a control group of usual care or attention control. The main outcome was glycemic control measured by percentage of glycated hemoglobin (HbA1c). Secondary outcomes included psychosocial functioning, diabetes knowledge, adverse and other clinical outcomes. A narrative synthesis and meta-analysis were conducted. Pooled effect sizes of standardised mean difference (SMD) were calculated.

Results
Ten eligible trials of three educational and seven psycho-educational interventions were identified. Most interventions were delivered by non-psychologists and targeted adolescents with more than one year duration of diabetes. Meta-analysis of nine of these trials (N = 1,838 participants) showed a non-significant reduction in HbA1c, attributable to the intervention (pooled SMD = -0.06, 95% CI: -0.21 to 0.09). Psycho-educational interventions aiming to increase child self-efficacy had a moderate, beneficial effect (SMD = 0.50, 95% CI: 0.13 to 0.87). No benefits on diabetes knowledge and other indicators of psychosocial functioning were identified.

Conclusions
There is insufficient evidence to recommend the use of particular psycho-educational programme for CYP with T1D in the UK. Further trials with sufficient power and reporting...
Introduction

Type 1 Diabetes (T1D) is one of the most common chronic diseases in childhood and adolescence, with an incidence of 28.2 new cases per 100,000 children under the age of 14 in the United Kingdom (UK) every year [1]. The UK has the fourth largest paediatric diabetes population in Europe and the fifth largest paediatric diabetes population in the world [2, 3] with the most recent estimates indicating at least 20,000 children under 19 years have T1D in the country [1-4].

In the UK, children and young people (CYP) with T1D are usually managed by multi-disciplinary teams in hospital-based diabetes clinics. T1D management primarily aims to optimise glucose control, whilst also maintaining quality of life. The gold standard for assessing average glucose control over the preceding 2–3 months is glycated Haemoglobin A1c (HbA1c) and regular testing is recommended to guide management advice. The National Institute for Health and Care Excellence (NICE) has recently recommended a target for HbA1c of 6.5% (48 mmol/mol) or lower [5]. Although it is widely accepted that intensive management aiming for lower glycaemic targets confers a significant reduction in risk of diabetes-related complications [6], only 6.4% of children cared for in clinical services in England and Wales meet this target [6].

Although the mainstay of T1D management is through insulin and dietary modifications, the need for structured educational programs at diagnosis has been highlighted as a priority by government bodies and diabetes organisations in the UK [6, 7]. Such programs constitute an integral part of diabetes management since they are necessary to integrate the complex demands of diabetes self-management into daily life. However, it is well accepted that education is a necessary, but not sufficient component of diabetes care. A distinction has been made between traditional education programs that aim to teach diabetes-related knowledge and skills, and those that incorporate psychological elements and provide support in areas such as problem-solving, goal-setting, stress management, coping, motivation, and counselling. Although a successful educational program has been introduced across the UK for adults with T1D [10-12], there is a lack of evidence-base for equivalent programs for children and adolescents with no agreed standardised package available in the UK [12].

Over the last few years several systematic reviews have examined the effect of these programs on metabolic and psychological outcomes in CYP with T1D. In a review commissioned by the NHS Health Technology Assessment Programme in 2001, Hapson et al. made the first comprehensive attempt to systematically review literature on the effectiveness of psycho-educational interventions among adolescents [13]. They summarised intervention effects using the standardised mean difference (SMD) (i.e., difference in mean change from baseline score between groups divided by the pooled standard deviation) which allows for a direct comparison across trials that used different scales to assess outcomes. They concluded that psycho-educational interventions had a small, non-significant effect on glycaemic control corresponding to a decrease of 0.6% in HbA1c (SMD = 0.3, 95% CI: 0.04 to 0.57) but appeared to
confer more substantial improvements in psychological outcomes (SMD = 0.4, 95% CI 0.2 to 0.6) [13]. The review also highlighted that evidence was predominantly derived from the USA with a notable shortage of UK-based randomised controlled trials (RCTs). An updated review by Murphy et al. in 2006 showed little progress in the development of new interventions in the UK [14]. Two subsequent meta-analyses provided evidence for a glycemic benefit of such interventions. The first showed that children and adolescents who received a psychological intervention had reduced HbA1c levels (SMD = -0.35, 95% CI [-0.66 to -0.04]) and psychological distress (SMD = 0.5, 95% CI: 0.8 to 0.1) compared to controls [15]. The second meta-analysis focused on family-based psycho-educational interventions and found a beneficial effect on both glycemic control (mean difference in % HbA1c = -0.6, 95% CI [-1.2 to -0.1]) and diabetes knowledge (SMD = 0.94, 95% CI 0.67 to 1.82) [16].

Evidence for the effectiveness of psycho-educational interventions in children with T1D is predominantly derived from non-UK trials. Only two small scale RCTs conducted in the UK were included in previous reviews [13, 16], the most recent of which was published in 2002 [17]. Yet, the evidence for the effectiveness of such interventions might be context-dependent since, for example, the quality of standard care against which interventions are compared shows considerable variation between countries [19]. This suggests that the extent to which conclusions from previous reviews can be generalised to the UK health care system is unclear.

Moreover, the last decade has also seen a number of large UK-based RCTs of psycho-educational interventions which have not been systematically reviewed. A need, therefore, exists for a comprehensive assessment of these interventions to determine whether there is sufficient evidence to support adoption of psycho-educational interventions into the NHS.

This systematic review aims to critically appraise and synthesize evidence from UK-based RCTs on the effectiveness of psychoeducational interventions in improving glycemic control, psychosocial functioning, diabetes knowledge and other outcomes in CYP with T1D. It is expected that findings of this review will be used to inform the evidence-base for adoption of such interventions into the NHS.

Methods

The protocol for this review has been published in the International Prospective Register for Systematic Reviews (PROSPERO) (Registration number: CRD42015040701 – see S1 File). The conduct and report of the current systematic review is in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) guidelines (see S1 Checklist) [20].

Search strategy

Six databases (Medline, Embase, Cochrane, PsycINFO, CINAHL, and Web of Science) were systematically searched for relevant citations published up until March 2016. The search strategy was developed with the assistance of a professional librarian. A combination of free-text words and medical subject heading (MeSH) terms were used to generate five subsets of citations relating to population, intervention, outcomes of interest, randomised controlled trials and studies conducted in the UK (see S2 File). Results were limited to CYP up to 24 years. The search was not limited by language or year of publication. A number of "snowballing" techniques were also used to minimise the potential of publication bias and to increase the sensitivity of our search. These included hand-searching reference lists of all selected articles, and contacting experts and corresponding authors of selected articles for any known published or unpublished relevant trials.
Eligibility criteria
We included trials conducted in the UK that examined the effectiveness of educational or psycho-educational interventions in CYP up to 26 years with T1D. A broad definition of psycho-educational interventions was used; we included interventions targeting CYP, their families and/or healthcare professionals that aimed to improve management of diabetes in children. Interventions including any type of teaching diabetes-related knowledge or skills and/or providing any form of psychosocial training or support were eligible. Studies were not excluded based on setting, delivery or duration of the intervention. Interventions had to be randomised controlled trials that involved a non-intervention arm of children with T1D receiving standard care. Trials in which the control group was matched for the extra contact time (attention control) were also included. Studies combining type 1 and type 2 diabetes or children and young people (<24 years old) with adults (≥24 years) were excluded unless results were stratified by type of diabetes or age group respectively. Finally, we excluded letters, commentaries, editorials, reviews, conference proceedings, intervention development protocols, pilot trials and qualitative studies.

Types of outcome measures
The primary outcome of interest was glycaemic control, as measured by levels of HbA1c. Secondary outcomes included indicators of psychosocial functioning, diabetes knowledge, insulin regimen, adverse events (episodes of hypoglycaemia and diabetes ketoacidosis-DKA), and service utilisation.

Study selection and data extraction
Retrieved citations were entered into a reference management library (EndNote), and duplicates were removed. Initially, titles and abstracts of unique citations were screened and full texts of potentially eligible articles were then retrieved and screened. Titles, abstracts, and full texts were independently reviewed by 2 reviewers (DC and CRH). In parallel, the same reviewers then independently extracted data from all eligible trials using a pre-piloted data extraction form (see S1 Table) as per guidelines by the Centre for Review and Dissemination (CRD) for systematic reviews in healthcare [21]. At all stages, any discrepancies were resolved by joint discussion. We extracted data on study design and methodology; intervention characteristics and type of care received by controls. We also extracted data on sample size, baseline characteristics, recruitment and study completion rates, reasons for attrition, power of the study, baseline and follow-up outcome data for each trial arm, and information for assessment of risk of bias. Corresponding authors of included studies were contacted by email for clarification on trial methods or data whenever there was insufficient data reported (three authors were contacted, all provided further information).

Interventions were categorised according to their primary methodology as educational (i.e. those targeting diabetes-related knowledge and skills); psychological (i.e. those providing any form of psychosocial support) or psycho-educational (those combining educational with psychological elements). Psycho-educational interventions were further classified into the following categories: supportive or counselling therapy (including motivational interviewing, non-directive counselling, and solution-focused therapy); cognitive-behavioural therapy (including techniques such as goal setting, activity scheduling, problem solving, cognitive restructuring, and stress management); family systems therapy; psychotherapy (including psychodynamic or interpersonal approaches) and other interventions (including eclectic approaches).
Quality assessment

Quality assessment was conducted independently by two reviewers (DM and KEH) and disagreements were resolved by consensus. Quality of individual trials was assessed using six domains of the Cochrane Collaboration's tool for assessing risk of bias [23], including sequence generation, allocation concealment, blinding of outcome assessors, completeness of outcome data, selective reporting of outcomes, and other sources of bias. Since blinding of participants and personnel to knowledge of the intervention was not possible, this domain was excluded from the assessment. Assessment of the two domains relating to blinding of outcome assessors and data completeness was made separately for glycaemic and psycho-educational outcomes. For each domain, studies were classified as being at low, high or unclear risk of bias.

Data synthesis and calculation of effect sizes

Data were analysed through narrative synthesis and meta-analysis. We used the SMD to summarise intervention effects on continuous outcomes, calculated by dividing the between-group difference in mean change from baseline scores (or follow-up scores adjusted for baseline values) by the pooled standard deviation of the change score [24]. We calculated the intervention effect using the follow-up interval set a priori for the definition of the primary outcome. Four trials provided multiple follow-up measurements without stating any primary time point, in which case we used the largest follow-up measurement available. To examine whether results were sensitive to selection of time point, we repeated the meta-analyses, where possible, by using the shortest follow-up measurement that was available immediately after the end of the intervention; no differences in the summary estimates were observed (see SI File). If standard deviations of change scores were not available from the published report, we obtained them by correspondence with the authors, or by hand calculating on the basis of available published data. For seven trials none of the above was feasible and standard deviations of change scores were imputed assuming a conservative correlation coefficient of 0.5 [24]. We varied the assumed correlation of r = 0.5 between baseline and follow-up measurements from r = 0.3 to r = 0.7 to see if this has any effect on the summary estimates; results were robust to these variations.

For trials with multiple intervention arms, the intervention arm which was directly comparable to the control arm (i.e., without any co-intervention or change in routine care) was chosen. In cross-over trial designs we only used data from the first period. For cluster randomised trials we used effect sizes adjusted for clustering effect and baseline values, or if not available, we adjusted sample sizes for the "design effect" [23].

To avoid unit of analysis errors, each trial contributed only one estimate per psychosocial construct. For example, where studies reported both patient and parent/carer reports of the same measure the former were used in the meta-analysis. Moreover, if studies reported multiple comparisons for different participants (such as for younger and older children), these measures were combined within each study before being entered in the meta-analysis. Finally, for comparisons that were not independent of one another (such as when studies reported several dimensions of quality of life for the same participants), we calculated a synthetic effect size for each study. This was defined as the weighted mean of the multiple effects with a variance that takes account of the correlation between the outcomes [25], again assuming it to be r = 0.5 if not stated.

Calculating overall summary effects

We combined effect sizes from individual studies using a random effects model to account for differences in the interventions and settings across studies. Results were provided as pooled
SMD with 95% confidence intervals. A standardized mean difference of -0.2, -0.5, and -0.8 was considered as small, medium, and large respectively [26]. To facilitate clinical interpretation of intervention effects on glycaemic control, we re-expressed the pooled SMD into absolute units by multiplying the estimate by the pooled standard deviation of all included studies. We generated forest plots, sorted by level of precision, to visually assess intervention effects across studies. All analyses were performed using STATA 12 (StataCorp, College Station, Texas).

**Assessment of heterogeneity and publication bias**

Heterogeneity between studies was assessed by the I² statistic, which quantifies the percentage of total variation that can be attributed to heterogeneity [22, 27]. Values of I² ≤ 50%, 50–75%, and ≥ 75% were considered indicative of low, moderate and high heterogeneity respectively [27]. Individual studies were removed one at a time from the meta-analysis to explore whether heterogeneity could be reduced. We also investigated potential sources of heterogeneity by conducting subgroup analyses, where possible, against potentially modifying factors (type of intervention, study quality and age group). Funnel plot was constructed to explore the possibility of publication bias for the primary outcome.

**Results**

The search strategy yielded 1,180 potentially relevant papers, of which 74 were read in full. Two additional articles were identified from reference lists. As per the eligibility criteria, we excluded a small pilot trial which examined the feasibility of a UK psychological intervention [29]. Results of the same intervention were reported in a subsequent main trial which was included in the current review [30]. In total, eleven studies [17, 18, 20–22] representing ten randomised controlled trials were found to meet the eligibility criteria and were included in the current review (see Fig 1).

Characteristics of included RCTs are shown in Table 1 and S5 File. In all RCTs participants were analysed by intention to treat. Six trials had a parallel group design [17, 20, 21, 23–25], one trial had a cross-over design [18] and three were cluster randomised [26, 27, 28]. Sample sizes ranged from 48 to 693 with a median of 113. Participation rates were generally low, ranging from 31% to 70.2% (median 50%). Six studies recruited only adolescents [17, 20, 21, 23, 24, 28] one of which also included young people up to 24 years [17]. All but one trial included children who had been diagnosed with T1D for more than one year. Median duration of diabetes was 5.6 years and ranged from 2.8 to 9.2 years.

Of the ten RCTs, seven [17, 20–22] used psychological and three [18, 23, 26] purely educational interventions. Six trials [19, 22, 23, 25] provided reference to the full trial protocol. However, in only four trials [20, 22, 25, 26] was the intervention described in sufficient detail to be replicated in practice. In all RCTs control groups received standard care which in most cases included three to five clinic visits per year; however, in one trial [21] the control group was matched for contact time by receiving additional support visits. Only one trial [22] provided a detailed description of standard care.

All psycho-educational interventions reported using an underlying theoretical model. Of the seven psycho-educational interventions, three used supportive or counseling therapy [21, 22, 25], two employed cognitive behaviour therapy strategies [17, 24], one used family therapy [20], and one used an eclectic approach. Interventions targeted individual children [17, 21, 23, 25, 26], groups of children [26], family groups [18, 20, 22, 23], and parents [32]. Four interventions [17, 22, 23, 26] were delivered in clinics and six [17, 18, 22, 23, 24–26] in home or other community settings. Intensity of interventions varied considerably with total time spent on
Relevant Citations Identified from Database Searching \( (n = 1,498) \)
- Medline \( (n = 232) \)
- Embase \( (n = 277) \)
- Cochrane \( (n = 194) \)
- PsychINFO \( (n = 25) \)
- CINAHL \( (n = 260) \)
- Web of Science \( (n = 425) \)

Duplicates Removed \( (n = 309) \)

Titles and Abstracts Screened for Meeting Eligibility Criteria \( (n = 1,189) \)

Articles Excluded \( (n = 1,115) \)

Full Text Articles Assessed for Eligibility \( (n = 74) \)

Articles Excluded \( (n = 65) \)
- Studies conducted outside the UK \( (n = 27) \)
- Protocols and intervention development reports \( (n = 5) \)
- Conference abstracts \( (n = 11) \)
- Adult population \( (n = 10) \)
- Non-randomised design \( (n = 4) \)
- No control group \( (n = 1) \)
- Pilot study \( (n = 1) \)
- Ineligible intervention \( (n = 4) \)

Articles Identified Through Hand-Search of Reference Lists \( (n = 2) \)

Articles Included in the Review \( (n = 11) \)
- Number of RCTs represented \( (n = 10) \)

Fig 1. Flow diagram of study selection.

https://doi.org/10.1371/journal.pone.0179865.g001
Table 1. Characteristics of included trials.

<table>
<thead>
<tr>
<th>First author (publication year)</th>
<th>Country (study name)</th>
<th>No of participants randomized (eligible for full trial analysis)</th>
<th>Mean (SD) %M. A. at baseline</th>
<th>Mean (SD) range of duration of diabetes (years)</th>
<th>Mean (SD) range of age (years)</th>
<th>Intervention, setting (mode of delivery)</th>
<th>Theoretical Model</th>
<th>Control group</th>
<th>Intervention start</th>
<th>Duration of intervention (in months) (except N/A)</th>
<th>Assessment points * (months)</th>
<th>Time in trial aspect on which analysis is based (in months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bown-Lee (2004)</td>
<td>Scotland</td>
<td>64 children &lt; 13 years with T1D ≥ 3 months</td>
<td>9.9 (1.3)</td>
<td>2.6 (2.7)</td>
<td>9.6 (3.3)</td>
<td>-</td>
<td>USSC</td>
<td>USSC</td>
<td>D</td>
<td>12</td>
<td>12 (13)</td>
<td>21 (13)</td>
</tr>
<tr>
<td>Howells (2003)</td>
<td>Scotland</td>
<td>79 children 12-15 years</td>
<td>8.6 (1.7)</td>
<td>7.0 (4.3)</td>
<td>10.9 (3.4)</td>
<td>Negotiated telephone support, Home, Child</td>
<td>SLT</td>
<td>USSC</td>
<td>D</td>
<td>12</td>
<td>12 (13)</td>
<td>21 (13)</td>
</tr>
<tr>
<td>Ferrelt (2009)</td>
<td>Scotland</td>
<td>64 girls (10th grade with T1D ≥ 3 years)</td>
<td>13.2 (1.9)</td>
<td>4.1 (1.7-4.9)</td>
<td>13.5 (12.5-15.5)</td>
<td>Automated text messaging support plus post-telephonic education (Home, Child)</td>
<td>SCT</td>
<td>USSC</td>
<td>D</td>
<td>12</td>
<td>12 (13)</td>
<td>N/A</td>
</tr>
<tr>
<td>Chiu et al. (2007)</td>
<td>Wales</td>
<td>50 adolescents 14-17 years with T1D ≥ 3 years</td>
<td>5.2 (1.6)</td>
<td>5.2 (1.6)</td>
<td>13.3 (1.9)</td>
<td>Motivational interviewing (Home, Child)</td>
<td>SLT</td>
<td>USSC</td>
<td>D</td>
<td>12</td>
<td>12 (13)</td>
<td>29 (9)</td>
</tr>
<tr>
<td>Murphy (2015)</td>
<td>UK (PACTS)</td>
<td>305 adolescents (70% with T1D ≥ 3 years)</td>
<td>9.3 (1.9)</td>
<td>5.5 (1.4)</td>
<td>15.2 (2.6)</td>
<td>Family-centered structured program, Child, (Home, Child, Family)</td>
<td>SLT</td>
<td>USSC</td>
<td>D</td>
<td>12</td>
<td>12 (13)</td>
<td>50 (13)</td>
</tr>
<tr>
<td>Gearing (2013)</td>
<td>UK (DEPCTED)</td>
<td>200 children 6-10 years with T1D ≥ 3 years</td>
<td>6.0 (1.6)</td>
<td>6.1 (2.7)</td>
<td>10.0 (2.6)</td>
<td>Training healthcare practitioners in consultation skills using electronic support, Child, Child and peer support</td>
<td>CMCS</td>
<td>USSC</td>
<td>D</td>
<td>12</td>
<td>12 (13)</td>
<td>100 (13)</td>
</tr>
<tr>
<td>Coles et al. (2013)</td>
<td>US (CHOCO)</td>
<td>139 adolescents 10-19 years with T1D ≥ 3 years</td>
<td>8.9 (1.6)</td>
<td>6.9 (1.6)</td>
<td>15.4 (1.6)</td>
<td>Structured educational program, Child, Group and Family</td>
<td>-</td>
<td>US</td>
<td>D</td>
<td>12, 24</td>
<td>3, 6, 12, 24, 18 (9)</td>
<td>180 (9)</td>
</tr>
<tr>
<td>Dooley et al. (2013)</td>
<td>UK (Tape R)</td>
<td>99 (Parental involvement age 11-17 years)</td>
<td>8.5 (1.3)</td>
<td>5.1 (3.6)</td>
<td>13.5 (1.6)</td>
<td>Self-direct, web-based behavioral intervention, Home, Parent</td>
<td>SLT</td>
<td>USSC</td>
<td>D</td>
<td>12</td>
<td>2.3</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Chislett (2014)</td>
<td>England (CASADO)</td>
<td>300 children 6-13 years with T1D ≥ 3 years (85%)</td>
<td>13.0 (1.9)</td>
<td>5.9 (3.3)</td>
<td>13.7 (2.7)</td>
<td>Motivational interviewing, at institution and at home, Child therapy, Child, Group and Family</td>
<td>USSC</td>
<td>USSC</td>
<td>D</td>
<td>4</td>
<td>12 (24)</td>
<td>120 (4)</td>
</tr>
<tr>
<td>Pallas (2015)</td>
<td>UK (K2CSP)</td>
<td>240 adolescents 11-17 years with T1D ≥ 3 years</td>
<td>9.2 (1.7)</td>
<td>5.5 (2.0)</td>
<td>13.5 (1.5)</td>
<td>Text-based structured education, Child, Group and Family</td>
<td>-</td>
<td>USSC</td>
<td>N + O</td>
<td>5 days</td>
<td>9, 12, 24</td>
<td>42 (9)</td>
</tr>
</tbody>
</table>


* from start of intervention

https://doi.org/10.1371/journal.pone.0179885.g001
intervention ranging from 2.4 to 35 hours (median of 8.5 hours). Most interventions were delivered by dietitians and nurses and in one trial [17] the interventionist had a
groundwork in psychology. Evidence for training of the interventionist was provided in half of the trials [17, 30, 32, 36, 37].

Five interventions [17, 18, 31, 35, 37] had a duration of one year with the remaining interventions [19, 22, 34, 36] lasting for 6 months or less. Half of the trials had a follow-up assessment after the end of the intervention. Retention rates ranged from 43% to 100% and half of the trials [18, 31, 32–35] were deemed underpowered to detect an effect in their primary outcome. Six trials reported monitoring adherence to trial protocol [17, 31, 32, 34, 36, 37]. Eight trials [17, 18, 26–28, 36, 37] provided information on intervention attendance and in three of them [19, 22, 34] attendance rates were considered as potentially insufficient to demonstrate an intervention effect (see S1 File).

Risk of bias

Risk of bias assessment is presented in Fig 2. Risk of selection bias due to inadequate sequence generation was unclear in half of the trials [18, 31–33, 37] since method of randomisation was not reported by authors. Risk of bias due to poor allocation concealment could not be assessed in four trials [18, 30, 32, 35]. Although binding of participants and interventionists is not feasible in the context of psycho-educational interventions, risk of detection bias from outcome assessment was considered small for HbA1c (objectively measured) and for most of the psycho-educational outcomes (use of standardised scales). There was high risk of bias due to incomplete psychological data in three trials [19, 31, 33], which reflected the high attrition rate in this type of interventions. Five trials [18, 31, 33, 26, 37] did not report all psychological outcomes and were at high risk of selective outcome reporting. Other sources of bias included baseline imbalances not accounted for in the analyses [34] and inappropriate study design (cross-over) [18]. When all bias domains were considered together, one trial [18] scored low risk in only one domain, three trials [19, 31, 33] scored low risk in two or three bias categories, and the remaining studies [17, 22, 34–37] scored low risk in four or more domains (see S6 File).

Effectiveness of Interventions

Glycated haemoglobin (HbA1c). A total of nine RCTs [17, 18, 26–33, 35–37] including 1,838 participants assessed the effectiveness of educational and psycho-educational interventions in reducing HbA1c levels and were included in the meta-analysis. Effect sizes in four out
of the nine trials showed a reduction in HbA1c levels attributable to the intervention (see Fig. 3). The pooled analysis did not show a statistically significant glycemic benefit (pooled SMD = -0.06, 95% CI: -0.21 to 0.09). The intervention effect was equivalent to a reduction in HbA1c of 0.1% (95% CI: -0.04% to 0.2%). There was moderate heterogeneity between the studies ($I^2 = 59.9%$), which was fully explained by an early trial of an educational intervention [12] with a low methodological quality rating. Exclusion of this trial from the meta-analysis did not change the overall conclusion (SMD = -0.04, 95% CI: -0.13 to 0.09, $I^2 = 0%$). The intervention effect on HbA1c remained non-significant when subgroup analyses were performed for purely educational interventions (SMD = -0.17, 95% CI: -0.88 to 0.55, three studies pooled), psycho-educational interventions (SMD = 0.01, 95% CI: 0.01 to 0.02, six studies pooled), or interventions targeting adolescents (SMD = -0.05, 95% CI: -0.20 to 0.10, four studies pooled).

**Psychosocial functioning.** Interventions addressed various measures of psychosocial functioning (see SI Table). Four trials of one educational [56] and three psycho-educational interventions [15, 31, 59] measured the effect of interventions on increasing self-efficacy. Overall, all interventions produced a small, non-significant improvement in self-efficacy (SMD = 0.30, 95% CI: 0.16 to 0.45, $I^2 = 70.6%$). Heterogeneity was reduced when we removed the one educational intervention [56], when it was omitted, effect of psychoeducational interventions on self-efficacy increased in magnitude and became statistically significant (SMD = 0.59, 95% CI: 0.13 to 0.87, $I^2 = 27.8%$). There was no evidence for a beneficial effect of psycho-educational

<table>
<thead>
<tr>
<th>Number of</th>
<th>Follow-up</th>
<th>SMD (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>nCTI</td>
<td>patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>months</td>
<td>SMD (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Rabito</td>
<td>0.67</td>
<td>12</td>
<td>0.01 (-0.01, 0.02)</td>
</tr>
<tr>
<td>Murphy</td>
<td>0.05</td>
<td>12</td>
<td>0.08 (-0.20, 0.36)</td>
</tr>
<tr>
<td>Price</td>
<td>0.11</td>
<td>12</td>
<td>-0.11 (-0.34, 0.12)</td>
</tr>
<tr>
<td>Chinn</td>
<td>0.68</td>
<td>24</td>
<td>0.06 (-0.20, 0.37)</td>
</tr>
<tr>
<td>Provance</td>
<td>0.11</td>
<td>12</td>
<td>0.11 (-0.34, 0.56)</td>
</tr>
<tr>
<td>Cuadrado</td>
<td>0.18</td>
<td>12</td>
<td>0.18 (-0.01, 0.37)</td>
</tr>
<tr>
<td>Hennes</td>
<td>0.74</td>
<td>12</td>
<td>-0.74 (-0.95, 0.22)</td>
</tr>
<tr>
<td>Chinn</td>
<td>0.03</td>
<td>24</td>
<td>-0.38 (-0.67, 0.25)</td>
</tr>
<tr>
<td>D'Amore</td>
<td>0.71</td>
<td>12</td>
<td>-0.71 (-1.31, 0.01)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.78</td>
<td>12</td>
<td>-0.78 (-1.31, 0.05)</td>
</tr>
</tbody>
</table>

**Fig 3.** Random effects meta-analysis of changes scores in HbA1c (%) in psycho-educational intervention group compared with control group. Intervention effects calculated as Standardised Mean Difference (SMD) with 95% confidence interval. A negative effect indicates improved glycemic control attributable to intervention.

https://doi.org/10.1371/journal.pone.0172065.g003
Interventions on other indicators of psychosocial functioning, including diabetes-specific quality of life, general quality of life, psychological distress and family functioning (see Fig 1), showed no significant changes between the groups. These included loc ation control[21], patient empowerment[23], health care climate[24], and patient enablement[23].

### Diabetes Knowledge

Five trials (two educational[21] and four psycho-educational[17, 21, 22, 23]) measured diabetes-related knowledge using similar scales[20–21]. Four trials[17, 21, 22, 23] provided sufficient data for the meta-analysis. With a random-effects model, psycho-educational interventions were associated with a non-significant reduction in diabetes knowledge, in all cases measured immediately after the end of the intervention (SMD = −0.11, 95% CI: −0.45 to 0.23, I² = 40.9%). Heterogeneity between studies was fully explained by an early trial of an educational intervention which was the only one to show a beneficial effect.
One study could not be pooled in the meta-analysis but reported no difference in post-intervention knowledge scores between the two groups [31].

Adverse and other outcomes. Seven trials [17, 19, 20, 23, 25, 26, 28, 33, 34] reported on the incidence of DKA and hyperglycaemic hospital admissions but none reported any increase related to the intervention. Insulin requirements were assessed in six trials [17, 18, 23, 25, 26, 28] but data were not suitable for a meta-analysis. The majority of trials reported no change in insulin regimen [17, 18, 31] or in the proportion of children who moved to pump therapy during the intervention [31]. Only two trials targeting groups of families reported a significant increase in insulin dose [31] or in frequency of insulin adjustment [32] in the intervention group. One trial assessed whether intervention increased children dietary adherence [33] but found no change. Finally, four trials assessed the impact of interventions on health service utilisation, including clinic visits [32, 35, 36], hospital admissions or contacts [33, 35, 37], and emergency hotline utilisation [38], but none found any significant change.

Publication bias

Visual assessment of the funnel plot for HbA1c showed a slightly asymmetric scatter which was mainly attributable to the presence of one small outlier study with positive effect (see [39, 40]).

Discussion

We identified ten UK-based RCTs comparing psycho-educational interventions for improving management of T1D for CYP with a control group of usual care or attention control. Pooled data from nine of these trials showed that psycho-educational interventions conferred no glycaemic benefits over that achieved with standard care across the populations studied. The interventions used a wide variety of approaches, predominantly educational programs or interventions combining educational with psychological components. Interventions with psychological components aiming to increase children’s self-efficacy to deal with diabetes appeared to show a moderate beneficial effect, however, evidence for an improvement in other important indicators of psychological functioning, such as quality of life, psychological distress and family functioning was absent.

In contrast to our findings on the synthesis of UK-based interventions, two recent meta-analyses mostly based on trials from North America [13, 14] reported significant glycaemic benefits of psycho-educational interventions in children and adolescents corresponding to reductions in HbA1c by around half percentage point. They also provided evidence for significant psychological [15] and educational benefits [14]. There are a number of potential explanations for the discrepancies between our findings and that of previous reviews.

Firstly, previous reviews were mostly based on ‘efficacy’ trials conducted in non-clinical settings by specialist interventionists with a solid background in psychology or psychiatry. In contrast, most of the interventions conducted in the UK were more pragmatic trials and delivered by non-specialist practitioners, mostly nurses and dietitians, after receiving relevant training. In fact, we found that only one UK intervention was delivered by a psychologist [21]; this was a person-centred intervention of motivational interviewing and showed the greatest beneficial effect in psychological outcomes, whilst also showing a trend for HbA1c improvement. Two other UK interventions [32, 37] attempted to incorporate components of motivational interviewing into routine clinical practice by training non-psychotherapists, but showed no improvement on diabetes outcomes.

Some of the most successful psychological interventions in children with T1D have been delivered by persons with a background in psychology [42–44], which seems to suggest that the discipline, training and skills of the person delivering the intervention in a paediatric
population could have an impact on outcomes. Evidence from interventions on adults with Type 2 Diabetes indicates that psychological and general health professionals are equally effective in delivering psychological interventions [47], but there is little evidence available for childhood T1D. Given the shortage of psychologists in the UK diabetes service [48], ‘efficacy’ interventions may not be easily applied into routine clinical settings, yet it might be worthwhile to ensure that future interventions are delivered by rigorously trained personnel who have a sound understanding of both diabetes and psychological matters related to child teaching and learning.

Previous reviews also used different criteria for study selection, including trials in which the control group received care other than standard, including for example intensive insulin treatment or less intensive psychological treatment. One of the UK trials included in the current review [49] also included a third arm receiving both the psycho-educational intervention and intensive insulin therapy and found a significant reduction in HbA1c by 1% as compared to standard care alone. Although a different design would be needed to disentangle the effect of the intervention from that of intensive therapy, this finding indicates that psycho-educational interventions could facilitate the uptake of intensive therapy schemes potentially enhancing their glycaemic benefits. Similar conclusions have been supported by USA trials [45, 49] which showed that psychological interventions used as an adjunct to intensive treatment conferred significant, consistent benefits in both glycaemic and psychosocial outcomes as compared to intensive treatment alone.

Although a lack of evidence for any glycaemic or psychosocial benefit of psycho-educational interventions conducted in the UK might simply reflect an absence of any ‘real’ effect, there are other potential explanations for the negative findings. In most trials participation rates were poor which indicates that children entering trials might represent a population of children who already had a certain level of education and motivation in such a way that any additional intervention may not have a noticeable impact on their physical and psychological health (‘ceiling effect’). Even the observed improvements in self-efficacy did not translate into glycaemic benefits, in most cases, measured one year after the end of the intervention. A longer duration of the intervention with provision of extended, continuous support even after the end of the program together with a longer follow-up period might be required for the behavioural changes to have an effect on the metabolic parameters and translate into reductions in levels of HbA1c.

Findings of our review showed that most of the UK interventions are being offered to adolescents with more than one year duration of diabetes. This might be a potential reason for adolescents’ reluctance to participate as they tend to view such interventions as ‘non-essential’. Those individuals might have already established management strategies and behaviours that are difficult to challenge and change. Although targeting children with a shorter duration of diabetes can be challenging given the complex adaptation processes taking place, evidence from US trials suggests that implementation of psycho-educational programs earlier in the course of the disease can provide a more effective framework for such interventions [46, 51].

Low study enrolment and high withdrawal rates had also resulted in typically small sample sizes with only half of the UK trials having adequate power to detect an intervention effect. Since power calculations were mostly based on HbA1c, low sample size was particularly problematic for assessment of psycho-educational outcomes. Moreover, attendance rates were unsatisfactory and in some trials attendance was not considered sufficient to demonstrate any potential effect. Lack of intervention ‘reach’ is a potentially important factor in the effectiveness of such interventions, and this may highlight the need to develop new and innovative strategies to decrease patient burden and encourage patient commitment in future interventions.
Educational and psychological interventions conducted in the UK also showed considerable heterogeneity in their content, intensity, selection of outcomes and delivery. This review highlights that although all of the interventions were theoretically grounded, they are poorly described, particularly with regard to the components of the intervention and the type of standard care, making it difficult to be replicated in practice. Attrition and reporting bias, especially with reference to psychosocial outcomes, was an issue in some studies and may further complicate interpretation of findings.

This is the first focused review to systematically examine the effectiveness of UK-based psycho-educational interventions on CYP with T1D. We used a rigorous protocol with high sensitivity and specificity to detect included studies. Psychosocial outcomes were grouped into conceptually-homogeneous constructs, which allowed the examination of intervention effects across different aspects of psychosocial functioning. However, there are limitations. Firstly, our review was restricted to UK studies thus precluding us from making any direct comparisons between UK and non-UK interventions. Second, the variability in the scales used to measure psychological outcomes and the differences in follow-up between interventions have contributed to the observed heterogeneity across studies and warrant caution when interpreting the findings. Moreover, half of the included trials provided a single follow-up measurement which prevented us from meaningfully stratifying analyses by follow-up interval. We were also unable to assess the effect of interventions on long-term metabolic control since none of the included studies followed participants beyond two years. Third, the small number of studies did not allow us to formally examine potential moderators, such as age, duration of diabetes and type of intervention. Fourth, the current review was limited to published studies. Although a comprehensive literature search was conducted and a number of “snowballing” techniques were used to identify eligible randomised trials, the potential of publication bias cannot be excluded. Finally, as per the eligibility criteria, we excluded one pilot study of a UK intervention. Although some readers might consider this as a limitation, results of this small pilot study were in line with that of the subsequent main trial of the same intervention, which was incorporated into the current meta-analysis. Therefore, we believe that exclusion of this pilot study is unlikely to have affected our pooled estimates.

Conclusion

There is currently insufficient evidence to recommend the use of psycho-educational programmes for children and adolescents with T1D in the UK. Successful implementation of similar interventions in the USA and other countries seems to suggest that such interventions are not inherently ineffective, and evaluation of their impact on diabetes outcomes requires focusing attention on the context within which these are applied and on potential target populations. One difference between UK trials and other non-UK successful trials has been the involvement of psychologists in the delivery of psychological interventions, which may be relevant to the differing success observed. Future randomised controlled trials in the UK could potentially benefit by considering active involvement of psychological specialists in the delivery of psychologically informed interventions and provision of rigorous training of interventionists in psychological and clinical aspects of diabetes. Greater consideration could also be given to the early implementation of psycho-educational programs in newly diagnosed children and also to the provision of innovative strategies aiming to encourage patient engagement.

Supporting information

S1 Checklist. PRISMA Checklist.

(DOC)
S1 File. Prospero protocol.
(PDF)
S2 File. Search terms by database.
(DOCX)
S3 File. Data extraction form.
( DOCX)
S4 File. Sensitivity analysis.
( DOCX)
S5 File. Critical appraisal of RCTs included in the systematic review.
( DOCX)
S6 File. Outcome of risk of bias assessment by trial.
( DOCX)
S7 File. Scales used to measure psycho-educational outcomes in included trials.
( DOCX)
S8 File. Funnel plot of intervention effects in HbA1c in the included studies.
( DOCX)

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Effectiveness of UK-based psycho-educational interventions for children and young people with Type 1 Diabetes

References


