Lifestyle risk factors and infectious disease mortality, including COVID-19, among middle aged and older adults: Evidence from a community-based cohort study in the United Kingdom

Matthew N. Ahmadi [1]

Bo-Huei Huang [1]

Elif Inan-Eroglu [1]

Mark Hamer [2]

Emmanuel Stamatakis [1]

1) Charles Perkins Centre, School of Health Sciences, Faculty of Medicine and Health, The University of Sydney, NSW, Australia

2) Division of Surgery and Interventional Science, Faculty Medical Sciences, University College London, London, UK

Corresponding Author:

Matthew N. Ahmadi
Charles Perkins Centre, School of Health Sciences, Faculty of Medicine and Health
Level 6, 1 John Hopkins Drive
Camperdown, NSW 2006
Australia

Phone: +61 2 86278646
Email: matthew.ahmadi@sydney.edu.au

Word count: 4204

Abstract

In this community-based cohort study, we investigated the relationship between combinations of modifiable lifestyle risk factors and infectious disease mortality. Participants were 468,569 men and women (56.5 ± 8.1, 54.6% women) residing in the United Kingdom. Lifestyle indexes included traditional and emerging lifestyle risk factors based on health guidelines and best practice recommendations for: physical activity, sedentary behaviour, sleep quality, diet quality, alcohol consumption, and smoking status. The main outcome was mortality from infectious diseases, including pneumonia, and coronavirus disease 2019 (COVID-19). Meeting public health guidelines or best practice recommendations among combinations of lifestyle risk factors was inversely associated with mortality. Hazard ratios ranged between 0.26 (0.23-0.30) to 0.69 (0.60-0.79) for infectious disease and pneumonia. Among participants with pre-existing cardiovascular disease or cancer, hazard ratios ranged between 0.30 (0.25-0.34) to 0.73 (0.60-0.89). COVID-19 mortality risk ranged between 0.42 (0.28-0.63) to 0.75 (0.49-1.13). We found a beneficial dose-response association with a higher lifestyle index against mortality that was consistent across sex, age, BMI, and socioeconomic status. There was limited evidence of synergistic interactions between most lifestyle behaviour pairs, suggesting that the dose-response relationship among different lifestyle behaviours is not greater than the sum of the risk induced by each behaviour. Improvements in lifestyle risk factors and meeting public health guidelines or best practice recommendations could be used as an ancillary measure to ameliorate infectious disease mortality.

Keywords: Physical activity, sedentary behaviour, sleep, diet, alcohol, smoking, population cohort

1. Introduction

The increase in annual infectious disease cases and the proliferation of resistant strains of pathogens threatens the successful treatment of community acquired infections (Cassini et al., 2019; Marston et al., 2016; Tacconelli et al., 2018). An additional 60,900 deaths occur annually due to antimicrobial resistance across the United States and Europe, whilst the incidence of sepsis now exceeds 48 million cases worldwide (Gelband et al., 2015; Kadri, 2020; Rudd et al., 2020). Respiratory infections, such as pneumonia, are the leading cause of death in developing countries, and the largest contributor to the overall burden of disease in the world measured in disability adjusted life years (Ferkol and Schraufnagel, 2014; Nair et al., 2011). Among the detrimental effects of infectious diseases are significant decreases in quality of life for individuals, in addition to clinical and economic burden across communities. The direct costs of treating community acquired pneumonia is estimated to be between 3.7 to 12.1 billion USD annually, with an additional \$1.8 to \$3.6 USD billion in indirect costs of economic productivity losses (Song et al., 2011; Welte et al., 2012; Weycker et al., 2010). Most recently, severe acute respiratory syndrome coronavirus 2, which causes coronavirus disease 2019 (COVID-19) has led to a global health pandemic.

Severe progression of infectious diseases is associated with multiple lifestyle risk factors (Baik et al., 2000; Hamer et al., 2019). The role of lifestyle behaviours and risk of infectious disease mortality is becoming increasingly important. This requires a better understanding of the relationship between combinations of different lifestyle risk factors that may increase the risk of mortality. To date, studies have only examined the individual associations of lifestyle risk factors and infectious diseases (Hamer et al., 2019; Paulsen et al., 2017; Wang et al., 2017). For example, smokers have shown an increased risk of both bacterial and viral infection-related mortality (Carter et al., 2015; Huttunen et al., 2011), and poor diet quality has been associated with low resistance to infections (Ambrus and Ambrus, 2004; Gordon, 1968; Katona and Katona-Apte, 2008; Scrimshaw and SanGiovanni, 1997). Further, among individuals, who never drink alcohol or moderately drink, infectious disease risk does not differ; risk, however, increases substantially among heavy drinkers, leading to higher rates of morbidity and mortality (Rehm et al., 2010; Samokhvalov et al., 2010). Higher volumes of physical activity are associated with a lower incidence of infectious diseases and related mortality (Baik et al., 2000; Hamer et al., 2019). Most recently, physical inactivity, a history of smoking, and excessive alcohol consumption have been identified as lifestyle risk factors that contribute to increased risk of hospitalizations due to COVID-19. More than a 4-fold increase in hospitalisation was observed among participants engaging in all unfavourable behaviours (Hamer et al., 2020). The additive influence of multiple lifestyle behaviours against infection related mortality, remains unknown.

Prior literature suggests different lifestyle behaviours may have synergistic effects (Stamatakis et al., 2015; Xiao et al., 2014). The risk of immune-suppressive effects from an unhealthy lifestyle behaviour, such as physical inactivity, may be amplified by unhealthy sleep habits and high sedentary time. Among the possible consequences is an increased risk of hospitalisations and mortality events caused by respiratory infections (Fletcher et al., 2018; Ibarra-Coronado et al., 2015; Nieman et al., 2011; Opp and Krueger, 2015; Sallis et al., 2020). Studies that have observed inconsistent relationships between inadequate sleep duration and respiratory infections did not consider the role of sleep quality or the influence of combined lifestyle behaviours (Irwin, 2015; Prather and Leung, 2016). Considering that individual lifestyle risk factors may have an additive influence on mortality risk, investigating combinations of lifestyle behaviours together will elucidate more clinically relevant information (Ding et al., 2015; Dunstan et al., 2012; Hamer et al., 2014; Hamilton et al., 2007; Stamatakis et al., 2015).

To our knowledge, no studies have examined the associations between both established and emerging lifestyle risk factors, with infectious disease that include: physical activity, sedentary behaviour, sleep quality, diet quality, alcohol consumption, and smoking status. The aim of this study was to examine the association of combined lifestyle risk factor indexes and risk of infectious disease mortality, including mortality due to pneumonia and COVID-19.

2. Materials and Methods

2.1 Participants

The UK Biobank is a prospective cohort study which aims to investigate the genetic, lifestyle, and environmental causes of a range of diseases (Allen et al., 2012; Sudlow et al., 2015; UK Biobank, 2007). Between 2006 and 2010, 502,656 adults aged between 40 and 69 years (229,182 men and 273, 474 women) were recruited. All participants were registered with the UK National Health Service (NHS) and lived within ~40 km of 1 of the 22 study assessment centres. The UK Biobank invited ~9.2 million people to participate through postal invitation with a telephone follow-up, with a response rate of 5.7%. The UK Biobank has approval from the North West Multi-Centre Research Ethics Committee, the National Information Governance Board for Health and Social Care in England and Wales, and the Community Health Index Advisory Group in Scotland. In addition, an independent Ethics and Governance Council was formed in 2004 to oversee UK Biobank's continuous adherence to the Ethics and Governance Framework, which were developed for the study (http://www.uk-biobank.ac.uk/ethics/). All participants provided written informed consent.

Participants consented to the use of their de-identified data and access to their national health-related hospital and death records. Exclusions prior to the onset of analyses included participants who did not have complete/usable physical activity, sedentary behaviour, sleep, diet, alcohol consumption, and smoking history information (n =20,144). We then excluded any remaining participants with an incomplete covariate profile (n = 13,903).

2.2 Measurements

During the baseline recruitment visit, participants were asked to complete a self-administered touchscreen questionnaire, which included questions on socio-demographics and lifestyle exposures.

2.2.1 Physical activity: Physical activity was measured using the International Physical Activity Questionnaire (IPAQ) short form (Craig et al., 2003) and included items on frequency and duration of walking, moderate intensity activity, and vigorous intensity activity. Missing values for a category were imputed using multivariate imputation by chained equations (Buuren and Groothuis-Oudshoorn, 2010). Physical activity was expressed as MET-hrs/week and based on the IPAQ scoring procedure, participants who attained 600 MET-hrs/week met the physical activity guidelines of 150 minutes of moderate-vigorous physical activity a week (Bull et al., 2020). Participants were classified as inactive if they attained 0 MET-hrs/week, insufficiently active if they had less than 600 MET-hrs/week, and sufficiently active if they had at least 600 MET-hrs/week.

2.2.2 Sedentary time: Total sedentary time was based on three questions enquiring about daily hours of TV, PC screen-based activities and driving. Sedentary time was classified as high (> 7 hours/d), medium (4 to 7 hours/d) , or low (>=4 hours/d).(Chau et al., 2015, 2013)

2.2.3 Sleep quality*:* Sleep quality was assessed using five healthy sleep characteristics which included (Fan et al., 2020): Morning chronotype, sleep duration (7-9 hours), not usually insomnia, no snoring, and no frequent daytime sleepiness. Following the sleep quality scoring by Fan et al, participants were given a score of “1” for every question they answered “yes” (Fan et al., 2020). Component scores were summed and participants were classified as having poor sleep quality (score = 0 to 1), moderate sleep quality (score = 2 to 3), or good sleep quality (score = 4 to 5).

2.2.4 Diet Quality: Diet quality was assessed using a modified Alternate Healthy Eating Index (AHEI), which is based on foods and nutrients that have been shown to be predictive of disease (Chiuve et al., 2012). Participants are given a score of 0 to 10 for each food category and the scoring criteria for the AHEI is described in detail elsewhere (McCullough et al., 2002). For the current study, participants reported their daily diet in four categories: fruits, vegetables, whole grains, and portions of red meat/ processed meat. All the component scores were summed and participants were classified as having poor diet quality (score = 0 to 10), moderate diet quality (score = 11 to 30), and good diet quality (score = 31 to 40).

2.2.5 Alcohol consumption*:* Participants reported their alcohol drinking status as: Never drinker, ex-drinker, or current drinker. Participants who were current drinkers, were asked about average weekly consumption of wine, spirits, and beer intake. Based on current UK guidelines, participants were categorised as never drinkers, ex-drinkers, within guideline drinkers (<14 UK units of alcohol/wk; 1 unit = 8g of alcohol), or above guideline drinkers (≥14 UK units of alcohol/wk).(Health, 2016; Rosenberg et al., 2018)

2.2.6 Smoking status*:* Participants were asked to report their current smoking status. They were classified as never smokers, previous smokers, and current smokers.

2.2.7 Healthy Lifestyle Index*:* Each lifestyle behaviour, except for alcohol consumption, was assigned a score ranging from zero (least healthy behaviour) to two (most healthy behaviour). Alcohol consumption was categorized into four groups on the basis that ex-alcohol drinkers are generally at a higher risk of all-cause mortality than lifelong never drinkers (Knott et al., 2015; Perreault et al., 2017).

Table 1 describes the categorisation for all six lifestyle risk factors and the corresponding scores that were assigned to participants. All six individual lifestyle behaviour scores were added together to obtain a healthy lifestyle index score. Never drinkers and guideline drinkers were given the same index score because the behaviours have both been shown to have similar protective health benefits (Friedman and Klatsky, 1993). A lifestyle behaviour score of 0-4 represented the least healthy group and was an indication that participants had a score of 0 in multiple behaviour categories without a score of 2 in more than two categories. A score of 10-12 represented the healthiest group, and was an indication that participants had a score of 2 in at least four out of the six categories.

--Insert Table 1 near here--

2.3 Outcomes

Participant data was linked to the national datasets from the National Health Service (NHS) Information Centre (England and Wales) and the NHS Central Register Scotland (Scotland). Complete follow-up was available through June 28th, 2020. Mortality incidence data were coded using the 10th Revision of the International Classification of Diseases (ICD-10) and included if it was the underlying or contributory cause of death. Infectious disease mortality was identified using the following ICD-10 codes: A00-B99 and J09-J18 (pneumonia). COVID-19 mortality was identified using ICD-10 codes U07.1-U07.2.

2.4 Statistical analyses

Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression models for individual lifestyle risk factors and healthy lifestyle index with infectious disease outcome. The reference group for each individual lifestyle risk factor was the least favourable lifestyle behaviour. The timescale was in calendar time (months). Multivariable proportional regression models were adjusted for the following covariates: age at baseline, sex, socioeconomic status based on the Townsend deprivation index (Townsend et al., 1988), ethnicity (White, South Asian, Black, Chinese, and other), body mass index (weight divided by squared height), corticosteroid use, and comorbidities (cardiovascular diseases, cancers, diabetes, chronic respiratory disease [ICD-10 codes J.40 to J.47], liver disease, end-stage renal disease, immune disorders/HIV, and hypertension defined as ≥140/90 mmHg)

To examine the associations between individual lifestyle risk factors and healthy lifestyle index with COVID-19 mortality, we used binomial regression to account for all mortality events occurring only between March to June 2020. The adjusted risk ratio models included all the covariates previously listed.

To evaluate the consistency of our findings in different population subgroups, we conducted a set of stratified analysis by: sex (male; female); age (< 50 years; < 60 years; and ≥ 60 years); body mass index (BMI) category (normal weight; overweight; obese); and socioeconomic status (Townsend index quintiles). In addition, we examined the associations among participants who had a history of cardiovascular disease and cancer. Three measures were used to investigate interaction between pairs of lifestyle behaviours: The relative excess risk due to interaction (RERI); attributable proportion due to interaction (AP); and the synergistic effects (S). RERI and AP would be equal to zero and S would be equal to 1 if there is no interaction present between pairs of behaviours (Andersson et al., 2005; Källberg et al., 2006). To reduce the possibility of spurious associations due to reverse causation, we repeated analyses after excluding all participants who died in the first five years of follow-up. Sensitivity analysis was conducted for infectious disease mortality by excluding all infectious disease mortality due to pneumonia. In another set of sensitivity analyses, we excluded participants with a history of smoking, cardiovascular disease, and cancer and included self-reported health as a covariate. We also assessed the associations of individual lifestyle risk factors with mortality among participants who had the least healthy lifestyle index score. All analysis was performed using R software (version 4.0.2).

3. Results

3.1 Sample

Our analysis included 468,569 participants. Supplemental Figure 1 provides a detailed flowchart of participants who were excluded due to missing or unusable data. The participants included in the study had a corresponding 4,176 deaths due to infectious diseases and 3,170 deaths due to pneumonia. There were an additional 387 deaths due to COVID-19. The number of participants with an event for each type of infectious disease is listed in Supplemental Table 1. The absolute risk and person-time rate for each healthy lifestyle index category is displayed in Supplemental Table 13. Table 2 presents the characteristics of the population at baseline. The median follow-up time was 11.3 years (IQR: 10.5 to 11.9 years) with a total of 5,166,793 person-years of follow-up before death or censoring, and 54.6% of the participants were female. The average age of participants at baseline was 56.5 (± 8.1) years. Among the 29,281 participants classified as having the lowest healthy lifestyle behaviour index score (0 to 5 score), 62.7% were inactive, 41.9% reported more than 7 hours per day in discretionary sedentary time, and 14.4% had poor sleep quality. Among these participants, 53.8% had poor diet quality, 45.8% were current smokers, and 87.3% were ex-drinkers or consuming more than 14 units of alcohol per week. Healthy lifestyle behaviour index scores were more prevalent among females, those with lower body mass index, and higher socioeconomic status.

--Insert Table 2 near here--

3.2 Individual lifestyle risk factors

3.2.1 Infectious disease and pneumonia mortality*:* The hazard ratios of each individual lifestyle behaviour for infectious disease and pneumonia mortality are provided in Tables 3 and 4, respectively. In the fully adjusted models, we found a direct association between all three movement behaviours (physical activity, sedentary behaviour, sleep) and infectious disease mortality and pneumonia mortality. When individuals with good sleep quality were compared to individuals with poor sleep quality, we observed a 20% decrease in infectious disease mortality (HR [95%CIs]: 0.80 [0.70 to 0.92]) and pneumonia mortality (0.80 [0.68 to 0.95]). The associations for sedentary time followed the same pattern, and when individuals with low sedentary time were compared to individuals with high sedentary time, we observed ≈21% decrease in infectious disease mortality (0.78 [0.72 to 0.87]) and pneumonia mortality (0.79 [0.67 to 0.94]). Comparatively, when individuals who were sufficiently active were compared to those who were inactive, we observed a 37% decrease in infectious disease mortality (0.64 [0.59 to 0.69]) and pneumonia mortality (0.63 [0.58 to 0.69]) (Tables 3 and 4).

Individuals who were ex-smokers or had never smoked had a significantly lower risk for infectious disease mortality (ex-smokers: 0.50 [0.46 to 0.54]; never smokers: 0.37 [0.34 to 0.41]) and pneumonia mortality (ex-smokers: 0.46 [0.42 to 0.51]; never smokers: 0.33 [0.30 to 0.36]) compared to individuals who were current smokers. In contrast, there was weak evidence for an association of diet quality. Compared to those with the poorest diet quality (referent group), only participants with good diet quality had an attenuated risk for infectious disease mortality (0.85 [0.77 to 0.93]) and pneumonia mortality (0.82 [0.75 to 0.91]). When ex-drinkers (referent group) were compared to current drinkers we observed a 44% to 47% reduction in infectious disease mortality (within guideline drinkers: 0.56 [0.50 to 0.63]; above guideline drinkers: 0.53 [0.47 to 0.60]).

--Insert Tables 3 and 4 near here--

3.2.2 COVID-19 mortality: Table 5 shows the risk ratio of each lifestyle behaviour category for COVID-19 mortality. In the fully adjusted models, individuals who were sufficiently active (RR [95%CIs]: 0.70 [0.54 to 0.89]), had never smoked (0.54 [0.39 to 0.74]), and were current drinkers (within guideline drinkers: 0.60 (0.40 to 0.89]; above guideline drinkers: 0.62 [0.41 to 0.93]) had lower COVID-19 mortality risk compared to the referent groups of each lifestyle risk factor.

--Insert Table 5 near here--

3.3 Healthy lifestyle index

3.3.1 Infectious disease and pneumonia mortality: Figure 1 shows the healthy lifestyle index hazard ratios for infectious disease and pneumonia mortality. For both infectious disease and pneumonia, there was a dose-response association with higher lifestyle index scores. For example, there was a 34% (HR [95%CIs]: 0.66 [0.59 to 0.75]) to 71% (0.29 [0.26 to 0.33]) reduction in infectious disease mortality for participants who were not classified in the least healthy behaviour group. Similarly, the pneumonia mortality risk was gradually attenuated with a higher lifestyle index; e.g. a 31% (0.69 [0.60 to 0.79]) to 74% (0.26 [0.23 to 0.30]) lower pneumonia mortality risk for participants when compared to those in the least healthy behaviour group. Additional analysis for infectious disease and pneumonia among only participants with cancer or cardiovascular disease showed a dose-response association with higher lifestyle index scores (Supplemental Figure 2 and 3). For infectious disease, participants with cancer had a 28% (0.72 [0.60 to 0.86]) to 65% (0.35 [0.29 to 0.42]) reduction in mortality risk, whilst participants with cancer had a 30% (0.72 [0.61 to 0.79]) to 68% (0.32 [0.28 to 0.37]) reduction compared to participants classified in the least healthy behaviour group. Likewise, the pneumonia mortality risk among was gradually attenuated with a higher lifestyle index; participants with cancer had a 27% (0.73 [0.60 to 0.89]) to 69% (0.31 [0.25 to 0.38]) reduction in mortality risk, and participants with cardiovascular disease had a 29% (0.71 [0.61 to 0.82]) to 70% (0.30 [0.25 to 0.34]) reduction.

--Insert Figure 1 near here --

3.3.2 COVID-19 mortality*:* Figure 2 displays the healthy lifestyle index risk ratios for COVID-19 mortality. Across the lifestyle groupings, we observed a similar reduction for COVID-19 mortality risk as in infectious disease and pneumonia mortality above. Among the 4th healthiest to healthiest lifestyle index, COVID-19 mortality risk was attenuated by 44% (RR [95% CIs]: 0.56 [0.38 to 0.82]) to 58% (0.42 [0.28 to 0.63]) for individuals who were not classified in the least healthy behaviour group.

--Insert Figure 2 near here –

3.3.3 Population impact: Supplemental Tables 2 to 11 and Supplemental Figures 2 to 3 display results stratified by sex, age, body mass index, socioeconomic status, and participants diagnosed with cardiovascular disease or cancer. There were generally consistent dose-response patterns with higher lifestyle indexes across all strata, including participants in the highest mortality risk groups. For example, participants in the lowest socioeconomic status quintile had an infectious disease mortality risk between 0.74 [0.59 to 0.92] to 0.31 [0.24 to 0.40]. Mortality risk among participants who were obese or over 60 years, and not classified in the lowest lifestyle index category was markedly low; among these participants, hazard ratios were between 0.70 [0.57 to 0.86] to 0.31 [0.20 to 0.47] for infectious disease mortality. Likewise, participants diagnosed with cardiovascular disease or cancer had an incremental decrease for mortality risk as the healthy lifestyle index improved with hazard ratios between 0.72 [0.60 to 0.85] to 0.32 [0.28 to 0.37]. The only pair of lifestyle behaviours that showed a statistically significant synergistic interaction (Supplemental Table 12) was not meeting physical activity guidelines and being a current smoker (RERI [95% CI] = 0.4 [0.06-0.8]; S = 1.3 [1.1-1.5], attributable portion due to interaction= 14.0% (2.8%-25.2%)]. The lack of significant synergistic interactions among most lifestyle behaviour pairs suggests that the dose-response relationship among the different lifestyle behaviours is not greater than the sum of the risk induced by each behaviour.

3.3.4 Sensitivity analysis: Removing participants with an event occurring in the first five years of follow-up, a history of smoking, cardiovascular disease, or cancer had no material impact on the dose-response associations with infectious disease mortality (Supplemental Tables 14 and 15, and Supplemental Figures 4 and 5). The associations of individual lifestyle risk factors with infectious disease mortality were not appreciably different when participants who had the least healthy lifestyle behaviour index score were analysed separately (Supplemental Tables 16 and 17). Three of the individual lifestyle risk factors showed beneficial associations against infectious disease mortality when pneumonia events were excluded: engaging in at least some physical activity; not being a current smoker; and consuming at least some alcohol (Supplemental Table 18).

4. Discussion

In this prospective cohort study, we examined the additive relationship between multiple lifestyle risk factors - physical activity, sedentary behaviour, sleeping quality, diet quality, alcohol consumption, and smoking. We found a clear beneficial dose response association with a healthier lifestyle index score against mortality from infectious disease, pneumonia, and COVID-19. These associations were independent of multiple markers of overall health status. We found limited evidence of synergistic interactions between pairs of behaviours, suggesting that any beneficial associations conferred by different lifestyle behaviours is not greater than the sum of the risk induced by each behaviour. This interpretation is supported by the results of the individual risk factors and outcomes. Results for COVID-19 mortality were consistent, although the low number of events made the statistical comparisons less clear. The patterns of attenuation, however, were comparable to infectious disease and pneumonia mortality. Our results are encouraging, not least for middle-aged and older adults who are at the highest risk of mortality from respiratory infections, who can potentially gain protection against the consequences of infectious disease through modifiable lifestyle behaviours.

We observed a dose-response for infectious disease mortality with higher lifestyle index scores. Infectious disease mortality in a smaller analysis of the Health Survey for England and Scottish Health Survey examining traditional lifestyle behaviours- that included physical activity, smoking, and alcohol consumption- reported protective associations against mortality among 97,844 participants if they engaged in at least some moderate to vigorous physical activity, and had never smoked (Hamer et al., 2019). The study did not examine the additive effects of lifestyle risk factors that led to a decrease in infectious disease mortality risk. Analysis of 64,027 HUNT Study participants showed that bloodstream-specific infectious disease mortality was associated with individual health behaviours, specifically moderate to vigorous physical activity levels and smoking status (Paulsen et al., 2017). Other epidemiological studies have assessed other traditional individual behaviours with infectious disease using various lifestyle behaviour measures (Almirall et al., 2008; Inoue et al., 2007; Wang et al., 2014). The current study is the first to examine the protective benefits for a combined healthy lifestyle and among individuals with comorbidities, who are most at risk of infectious disease mortality. The health benefits were found to be additive and can be attained through a combination of lifestyle behaviours. The dose-response nature of the associations between healthy lifestyle indexes was consistent across infectious disease, pneumonia, and COVID-19 mortality.

We found consistent beneficial associations for all six individual lifestyle behaviour categories with infectious disease and pneumonia mortality. With only one exception, however, there was no evidence of synergistic interactions between pairs of behaviours. Specifically, meeting physical activity guidelines and not being a current smoker were the only lifestyle behaviours to have a synergistic interaction against the risk of infectious disease mortality. Habitual moderate to vigorous physical activity enhances a number of immune parameters such as increasing natural killer cell activity, neutrophils, number of circulating lymphocytes, and cytokine production (Mackinnon, 1999; Matthews et al., 2002; Nieman, 1994; Nieman et al., 1990). Conversely, smoking affects many of the same immune-parameters but in the opposite direction (Hersey et al., 1983; Sopori, 2002).

Meeting health guidelines or best practice recommendations in combinations of different lifestyle behaviours can significantly reduce the risk of infectious disease mortality among both the low and high risk segments of the population, regardless of sex, age, weight, or socioeconomic status. In addition to preventive immunology measures, public health efforts focused on improvements in meeting minimum lifestyle recommendations could be used as an ancillary measure to ameliorate the most severe health consequences of infectious disease, especially among middle aged and older adults. Participants with existing chronic conditions such as cardiovascular disease and cancer— for whom our study has also shown to gain health benefits—might choose to engage in a number of differing healthy lifestyle behaviours and can still attain protective benefits against infectious disease, pneumonia, and COVID-19 mortality. These findings offer additional resources for primary care to prescribe improvements in lifestyle risk factors that can be used as a powerful ancillary measure against mortality from infectious disease.

To our knowledge, this is the first study to examine a comprehensive lifestyle risk factor index score incorporating multiple modifiable behaviours (physical activity, sedentary behaviour, sleep quality, diet quality, alcohol consumption, and smoking status) in relation to infectious disease mortality risk. We were able to provide a comprehensive assessment for sleep quality that accounted for five sleep characteristics. We were, also, able to separate never drinkers from ex-drinkers who may have quit drinking due to prior alcohol-related problems. The dietary measure was comprehensive and included fruits, vegetables, grains, and red/processed meat. We also did not conflate the lifestyle behaviours with their outcomes, as some lifestyle behaviour indices have previously done by including weight status or other metabolic health indicators in the index (Bonaccio et al., 2019; Lee et al., 2011). We examined modifiable lifestyle behaviours in a large cohort with more than 10 years follow-up for mortality, and the longest person-years follow-up in the field, and quantified the population health impact from different lifestyle behaviour combinations and synergistic interactions. The use of lifestyle behaviour indices such as ours based on current guidelines and best practice category thresholds for risk allows for policy-relevant lifestyle behaviours to be easily translated and assessed across settings and populations.

Opposing these strengths were several limitations. First, all lifestyle risk factors were measured with self-report questionnaires. Due to social desirability bias, misclassification is potentially non-random, and the results are most likely biased toward the null, with participants more likely to report desirable behaviours. Therefore, the preventable infectious disease mortality related to the healthy lifestyle indices is likely to be underestimated, as indicated by PF. Second, the sleep quality scoring included sleep chronotype, which might be influenced more by genetic traits than behavioural factors (Adan et al., 2012; Hur et al., 1998; Koskenvuo et al., 2007). Third, although the UK Biobank cohort is not representative of the general population (UK Biobank participants are healthier than the general population), prior epidemiological evidence has shown that there is little evidence for bias attributable to nonparticipation and exposure-disease relationships are widely generalizable (Fry et al., 2017). This reinforces the epidemiological principle that associations are less dependent on the representativeness of the cohort, relative to prevalence (Galea et al., 2007).

4.1 Conclusions

This large prospective cohort study examined the additive impact of healthy lifestyle behaviour combinations, which included the analysis of traditional and emerging lifestyle factors. We found that in middle aged and older adults, including those with cardiovascular disease and cancer, healthier lifestyle behaviours may protect against the most severe consequences of infectious disease. The findings based on public health guidelines and best practice recommendations provides information that clinicians and researchers can readily translate into practice and future research.

Declaration of competing interest

The authors declare that they have no competing interests

Acknowledgements

We are grateful to the UK Biobank participants. This research has been conducted using the UK Biobank Resource

References

Adan, A., Archer, S.N., Hidalgo, M.P., Di Milia, L., Natale, V., Randler, C., 2012. Circadian typology: A comprehensive review. Chronobiol. Int. 29, 1153–1175. https://doi.org/10.3109/07420528.2012.719971

Allen, N., Sudlow, C., Downey, P., Peakman, T., Danesh, J., Elliott, P., Gallacher, J., Green, J., Matthews, P., Pell, J., Sprosen, T., Collins, R., 2012. UK Biobank: Current status and what it means for epidemiology. Heal. Policy Technol. https://doi.org/10.1016/j.hlpt.2012.07.003

Almirall, J., Bolíbar, I., Serra-Prat, M., Roig, J., Hospital, I., Carandell, E., Agustí, M., Ayuso, P., Estela, A., Torres, A., De Salas, J.M., Costa, J., Tristany, M., Grau, M.J., Sancho, S., Miguel, E., Fradera, M., Ochoa, I., Castany, M.J., Quilez, A., Marina, V., Subias, P., Jimeno, B., Bradnovich, A., Rodriguez, M., Ramon, E., Gardella, A., Ginés, C., Mestres, X., Armada, A., Mallafré, J., Roger, M., Gros, M.T., Les, N., Joanola, J., Doménech, J., Bundó, M., Trilla, M., Massons, J., Montero, J., Zurilla, E., Torán, P., Aizpurua, M.M., Lozano, G., Casals, J., Sorribes, J., Torrellas, D., Anglada, J.L.L., Salabarnada, J., Sanz, E., Gorgas, F., Ribas, A., Fau, E., Pellicer, I., Morales, S., Casas, A., Bernad, J., De Montoliu, A., Gaya, J., Vallés, R., Vazquez, A., Peiró, R., Aresté, G., Mengual, G.N., Viñes, M.C., Almerich, E., Lopez, M.A., Bel, J., Gosalves, A., Macip, S., Carrillo, E., Paulo, P., Pol, M., Sala, J., Mir, P., Carrera, P., Legazpi, I., Planellas, F., Beltran, A., Planas, T., Rovira, J., De Ciurana, M., Xargay, C., Cortés, R.B., Paredes, J., Olive, J.G., Montoya, P., Burcet, F.X., Alcantarilla, D., De Ribot, J., Gorgot, M.R., Bas, R.A., Rosa, M.B., Castells, J., Castillo, J.A., Torrent, J.C., Rodríguez, D., Rius, X., Navarro, M., Benet, J.M., Caballero, J.C., Llach, J., Sanglas, J., Morales, V., Solanella, J., Cardona, J.I., Ferrer, J., Solís, M.J., Güerri, F., Murillo, M.J., Llovet, M.D., Guinea, I., Juáreztarrag, M.M., Alvarez, M., Bladé, J., Sánchez Oró, I., Martin, F., Cabré, J.J., Frigola, J., Boj, J., Chacon, A., Satué, E., Gallego, F., Montanyés, D., Basora, T., Martin, E., Gil, P., Roselló, M., Marimon, J., Costa, B., Gutiérrez, C., Moltó, E., Isach, A., Izzeddin, N., Campani, M., Ferré, J., Fernández, A., Jové, J., Vilalta, J., Ribera, E., Fernández, M., Ochoa, O., Vila Palacios, A., Donado-Mazarrón, A., Ramon, C., Caballol, R., Navarro, L., Masqué, J., Llor, L.L., Garcia, G., Arasa, M.J., Yoldi, A., Viloria, I., Vallespi, F., Clua, J.L.L., Basart, J.M., Ciurana, E., Monclus, J.F., Casanovas, A., Viñas, L., Checa, E., Marin, J., Santigosa, J., Arayo, F., Campillos, C., Juarez, A., Perez, J., Paredes, E., Rodriguez, J., Solà, Y., Pujol, J., Navarro, M.A., Casado, I., Madrid, M., Berdié, J., Andrés, M.J., Barragan, B., Torras, A., Gonzalez, S., Fuentes, A., El Hosn-Makarem, J.A., Pelaez, F., Ubieto, A., Fallada, A., Josa, A., Favà, E., Ros, M., Alonso, M., Pinazo, M.J., Borrás, S., Nolla, C., Bitrià, J., Araujo, O., Collado, A., Glaria, T., Montero, J.C., Flores, P., Serra, P., Torrellas, E., Buxadé, I., Mussoll, J., Gomez, M., Serrano, C., Pubill, M., Gost, J., Burdoy, E., Busquets, L.L., De Castro, S., Bartolomé, M., Corona, E., Valverde, R., Verde, Y., Alegre, M., Papiol, M., Martí, O., Catalá, M., Martinez, M.A., Diaz, E., Borrás, A., Aznar, F., Riera, F., Colom, I., Calvet, E., Nicolás, J., Ruiz, J., Mateu, C., Arranz, J., Fé, A., Puig, B., Gutiérrez, M., Morant, L.L., Llull, M., Estelrich, J., Quintana, L., Llabrés, C., Sureda, M.M., Cuevas, L., Muñoz, Y., Llobera, J., Iñiguez, M., Guasch, J., Sánchez, F., Pascual, J., Castelló, A., Gómez, L.L., Marin, P., Garcia, C., Moreno, P., Coll, M., Palma, C., Ribera, C., Aldosa, J., Alonso, C., Bergés, A., Burgués, J., Burgués, L.L., Busquets, J., Casal, D., Cerdán, N., Crespo, X., Duat, R., Escoda, J., Fiter, M., Font, A., Fraysse, M., Fuentes, S., García-Núñez, R., López-Pinacho, T., Masardo, M., Martínez-Illescas, J., Morisset, P., Pallarés, M., Pérez-Serra, R., Plà, A., Pons, E., Ruiz, A., Rodríguez-Picart, J.C., Sánchez-Claver, J., Sylvestre, E., Tolosa, R., Touceda, J.A., Varela, J.R., Vidal, J.C., 2008. New evidence of risk factors for community-acquired pneumonia: A population-based study. Eur. Respir. J. 31, 1274–1284. https://doi.org/10.1183/09031936.00095807

Ambrus, J.L., Ambrus, J.L., 2004. Nutrition and infectious diseases in developing countries and problems of acquired immunodeficiency syndrome. Exp. Biol. Med. 229, 464–472. https://doi.org/10.1177/153537020422900603

Andersson, T., Alfredsson, L., Källberg, H., Zdravkovic, S., Ahlbom, A., 2005. Calculating measures of biological interaction. Eur. J. Epidemiol. 20, 575–579. https://doi.org/10.1007/s10654-005-7835-x

Baik, I., Curhan, G.C., Rimm, E.B., Bendich, A., Willett, W.C., Fawzi, W.W., 2000. A prospective study of age and lifestyle factors in relation to community-acquired pneumonia in US men and women. Arch. Intern. Med. 160, 3082–3088. https://doi.org/10.1001/archinte.160.20.3082

Bonaccio, M., Di Castelnuovo, A., Costanzo, S., De Curtis, A., Persichillo, M., Cerletti, C., Donati, M.B., de Gaetano, G., Iacoviello, L., Investigators, M.S., 2019. Impact of combined healthy lifestyle factors on survival in an adult general population and in high-risk groups: prospective results from the Moli-sani study. J. Intern. Med. 286, 207–220. https://doi.org/10.1111/joim.12637

Bull, F., Saad Al-Ansari, S., Biddle, S., Borodulin, K., Buman, M., Cardon, G., Carty, C., Chaput, J.-P., Chastin, S., Chou, R., Dempsey, P., DiPietro, L., Ekelund, U., Firth, J., Friedenreich, C., Garcia, L., Gichu, M., Jago, R., Katzmarzyk, P., Lambert, E., Leitzmann, M., Milton, K., Ortega, F., Ranasinghe, C., Stamatakis, E., Willumsen, J., 2020. World Health Organization 2020 Guidelines on Physical Activity and Sedentary Behaviour. Br. J. Sports Med. 1451–1462. https://doi.org/10.1136/bjsports-2020-102955

Buuren, S. van, Groothuis-Oudshoorn, K., 2010. mice: Multivariate imputation by chained equations in R. J. Stat. Softw. 1–68. https://doi.org/10.1080/10580530.2013.739883

Carter, B.D., Abnet, C.C., Feskanich, D., Freedman, N.D., Hartge, P., Lewis, C.E., Ockene, J.K., Prentice, R.L., Speizer, F.E., Thun, M.J., Jacobs, E.J., 2015. Smoking and Mortality — Beyond Established Causes. N. Engl. J. Med. 372, 631–640. https://doi.org/10.1056/nejmsa1407211

Cassini, A., Högberg, L.D., Plachouras, D., Quattrocchi, A., Hoxha, A., Simonsen, G.S., Colomb-Cotinat, M., Kretzschmar, M.E., Devleesschauwer, B., Cecchini, M., Ouakrim, D.A., Oliveira, T.C., Struelens, M.J., Suetens, C., Monnet, D.L., Strauss, R., Mertens, K., Struyf, T., Catry, B., Latour, K., Ivanov, I.N., Dobreva, E.G., Tambic Andraševic, A., Soprek, S., Budimir, A., Paphitou, N., Žemlicková, H., Schytte Olsen, S., Wolff Sönksen, U., Märtin, P., Ivanova, M., Lyytikäinen, O., Jalava, J., Coignard, B., Eckmanns, T., Abu Sin, M., Haller, S., Daikos, G.L., Gikas, A., Tsiodras, S., Kontopidou, F., Tóth, Á., Hajdu, Á., Guólaugsson, Ó., Kristinsson, K.G., Murchan, S., Burns, K., Pezzotti, P., Gagliotti, C., Dumpis, U., Liuimiene, A., Perrin, M., Borg, M.A., de Greeff, S.C., Monen, J.C., Koek, M.B., Elstrøm, P., Zabicka, D., Deptula, A., Hryniewicz, W., Caniça, M., Nogueira, P.J., Fernandes, P.A., Manageiro, V., Popescu, G.A., Serban, R.I., Schréterová, E., Litvová, S., Štefkovicová, M., Kolman, J., Klavs, I., Korošec, A., Aracil, B., Asensio, A., Pérez-Vázquez, M., Billström, H., Larsson, S., Reilly, J.S., Johnson, A., Hopkins, S., 2019. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect. Dis. 19, 56–66. https://doi.org/10.1016/S1473-3099(18)30605-4

Chau, J.Y., Grunseit, A., Midthjell, K., Holmen, J., Holmen, T.L., Bauman, A.E., Van Der Ploeg, H.P., 2015. Sedentary behaviour and risk of mortality from all-causes and cardiometabolic diseases in adults: Evidence from the HUNT3 population cohort. Br. J. Sports Med. 49, 737–742. https://doi.org/10.1136/bjsports-2012-091974

Chau, J.Y., Grunseit, A.C., Chey, T., Stamatakis, E., Brown, W.J., Matthews, C.E., Bauman, A.E., Van Der Ploeg, H.P., 2013. Daily sitting time and all-cause mortality: A meta-analysis. PLoS One 8, 1–14. https://doi.org/10.1371/journal.pone.0080000

Chiuve, S.E., Fung, T.T., Rimm, E.B., Hu, F.B., McCullough, M.L., Wang, M., Stampfer, M.J., Willett, W.C., 2012. Alternative dietary indices both strongly predict risk of chronic disease. J. Nutr. 142, 1009–1018. https://doi.org/10.3945/jn.111.157222

Craig, C.L., Marshall, A.L., Sjöström, M., Bauman, A.E., Booth, M.L., Ainsworth, B.E., Pratt, M., Ekelund, U., Yngve, A., Sallis, J.F., Oja, P., 2003. International physical activity questionnaire: 12-Country reliability and validity. Med. Sci. Sports Exerc. 35, 1381–1395. https://doi.org/10.1249/01.MSS.0000078924.61453.FB

Ding, D., Rogers, K., van der Ploeg, H., Stamatakis, E., Bauman, A.E., 2015. Traditional and Emerging Lifestyle Risk Behaviors and All-Cause Mortality in Middle-Aged and Older Adults: Evidence from a Large Population-Based Australian Cohort. PLoS Med. 12, 1–21. https://doi.org/10.1371/journal.pmed.1001917

Dunstan, D.W., Howard, B., Healy, G.N., Owen, N., 2012. Too much sitting - A health hazard. Diabetes Res. Clin. Pract. 97, 368–376. https://doi.org/10.1016/j.diabres.2012.05.020

Fan, M., Sun, D., Zhou, T., Heianza, Y., Lv, J., Li, L., Qi, L., 2020. Sleep patterns, genetic susceptibility, and incident cardiovascular disease: A prospective study of 385 292 UK biobank participants. Eur. Heart J. 41, 1182–1189. https://doi.org/10.1093/eurheartj/ehz849

Ferkol, T., Schraufnagel, D., 2014. The global burden of respiratory disease. Ann. Am. Thorac. Soc. 11, 404–406. https://doi.org/10.1513/AnnalsATS.201311-405PS

Fletcher, G.F., Landolfo, C., Niebauer, J., Ozemek, C., Arena, R., Lavie, C.J., 2018. Promoting Physical Activity and Exercise: JACC Health Promotion Series. J. Am. Coll. Cardiol. 72, 1622–1639. https://doi.org/10.1016/j.jacc.2018.08.2141

Friedman, G.D., Klatsky, A.L., 1993. Is alcohol good for your health? N. Engl. J. Med. 1882–1883.

Fry, A., Littlejohns, T.J., Sudlow, C., Doherty, N., Adamska, L., Sprosen, T., Collins, R., Allen, N.E., 2017. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. Am. J. Epidemiol. 186, 1026–1034. https://doi.org/10.1093/aje/kwx246

Galea, S., Ph, D.R., Tracy, M., 2007. Participation Rates in Epidemiologic Studies. Ann. Epidemiol. 17, 643–653. https://doi.org/10.1016/j.annepidem.2007.03.013

Gelband, H., Miller-Petrie, M., Pant, S., Gandra, S., Levinson, J., Barter, D., White, A., Laxminarayan, R., 2015. The state of the world's antibiotics 2015. Wound Heal. South. Africa 8, 30–34.

Gordon, J.E., 1968. Weanling diarrhoea—a synergism of infection and nutrition, in: Interactions of Malnutrition and Infection. p. 216.

Hamer, M., Kivimäki, M., Gale, C.R., Batty, G.D., 2020. Lifestyle risk factors, inflammatory mechanisms, and COVID-19 hospitalization: A community-based cohort study of 387,109 adults in UK. Brain. Behav. Immun. 87, 184–187. https://doi.org/10.1016/j.bbi.2020.05.059

Hamer, M., O'Donovan, G., Stamatakis, E., 2019. Lifestyle risk factors, obesity and infectious disease mortality in the general population: Linkage study of 97,844 adults from England and Scotland. Prev. Med. (Baltim). 123, 65–70. https://doi.org/10.1016/j.ypmed.2019.03.002

Hamer, M., Stamatakis, E., Steptoe, A., 2014. Effects of substituting sedentary time with physical activity on metabolic risk. Med. Sci. Sports Exerc. 46, 1946–1950. https://doi.org/10.1249/MSS.0000000000000317

Hamilton, M., Hamilton, D., Zderic, T., 2007. Role of low energy expenditure and sitting in obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease. Diabetes 56, 2655–2667. https://doi.org/10.2337/db07-0882.CVD

Health, D. of, 2016. Alcohol guidelines review–Report from the Guidelines development group to the UK Chief Medical Officers.

Hersey, P., Prendergast, D., Edwards, A., 1983. Effects of cigarette smoking on the immune system Follow-up studies in normal subjects after cessation of smoking. Med. J. Aust. 2, 425–429. https://doi.org/10.5694/j.1326-5377.1983.tb122565.x

Hur, Y.-M., Bourchar Jr, T., Lykken, D., 1998. Genetic and environmental influence on morningness-eveningness. Pers. Individ. Dif. 25, 917–925.

Huttunen, R., Heikkinen, T., Syrjänen, J., 2011. Smoking and the outcome of infection. J. Intern. Med. 269, 258–269. https://doi.org/10.1111/j.1365-2796.2010.02332.x

Ibarra-Coronado, E.G., Pantaleón-Martínez, A.M., Velazquéz-Moctezuma, J., Prospéro-García, O., Méndez-Díaz, M., Pérez-Tapia, M., Pavón, L., Morales-Montor, J., 2015. The Bidirectional Relationship between Sleep and Immunity against Infections. J. Immunol. Res. 2015. https://doi.org/10.1155/2015/678164

Inoue, Y., Koizumi, A., Wada, Y., Iso, H., Watanabe, Y., Date, C., Yamamoto, A., Kikuchi, S., Inaba, Y., Toyoshima, H., Tamakoshi, A., 2007. Risk and protective factors related to mortality from pneumonia among middle-aged and elderly community residents: The JACC study. J. Epidemiol. 17, 194–202. https://doi.org/10.2188/jea.17.194

Irwin, M.R., 2015. Why sleep is important for health: A psychoneuroimmunology perspective. Annu. Rev. Psychol. 66, 143–172. https://doi.org/10.1146/annurev-psych-010213-115205

Kadri, S.S., 2020. Key Takeaways from the U.S. CDC's 2019 Antibiotic Resistance Threats Report for Frontline Providers. Crit. Care Med. 939–945. https://doi.org/10.1097/CCM.0000000000004371

Källberg, H., Ahlbom, A., Alfredsson, L., 2006. Calculating measures of biological interaction using R. Eur. J. Epidemiol. 21, 571–573. https://doi.org/10.1007/s10654-006-9037-6

Katona, P., Katona-Apte, J., 2008. The interaction between nutrition and infection. Clin. Infect. Dis. 46, 1582–1588. https://doi.org/10.1086/587658

Knott, C.S., Coombs, N., Stamatakis, E., Biddulph, J.P., 2015. All cause mortality and the case for age specific alcohol consumption guidelines: Pooled analyses of up to 10 population based cohorts. BMJ 350. https://doi.org/10.1136/bmj.h384

Koskenvuo, M., Hublin, C., Partinen, M., Heikkilä, K., Kaprio, J., 2007. Heritability of diurnal type: A nationwide study of 8753 adult twin pairs. J. Sleep Res. 16, 156–162. https://doi.org/10.1111/j.1365-2869.2007.00580.x

Lee, C., Sui, X., Hooker, S.P., Ebert, J.R.H., Blair, S.N., 2011. Combined Impact of Lifestyle Factors on Cancer Mortality in Men. https://doi.org/10.1016/j.annepidem.2011.04.010

Mackinnon, L.T., 1999. Advances in exercise immunology. Human Kinetics.

Marston, H.D., Dixon, D.M., Knisely, J.M., Palmore, T.N., Fauci, A.S., 2016. Antimicrobial resistance. JAMA - J. Am. Med. Assoc. 316, 1193–1204. https://doi.org/10.1001/jama.2016.11764

Matthews, C.E., Ockene, I.R.A.S., Freedson, P.S., Rosal, M.C., Merriam, P.A., Hebert, J.R., 2002. Moderate to vigorous physical activity and risk of upper-respiratory tract infection. Med. Sci. Sport. Exerc. 34, 1242–1248.

McCullough, M.L., Feskanich, D., Stampfer, M.J., Giovannucci, E.L., Rimm, E.B., Hu, F.B., Spiegelman, D., Hunter, D.J., Colditz, G.A., Willett, W.C., 2002. Diet quality and major chronic disease risk in men and women: Moving toward improved dietary guidance. Am. J. Clin. Nutr. 76, 1261–1271. https://doi.org/10.1093/ajcn/76.6.1261

Nair, H., Brooks, W.A., Katz, M., Roca, A., Berkley, J.A., Madhi, S.A., Simmerman, J.M., Gordon, A., Sato, M., Howie, S., Krishnan, A., Ope, M., Lindblade, K.A., Carosone-Link, P., Lucero, M., Ochieng, W., Kamimoto, L., Dueger, E., Bhat, N., Vong, S., Theodoratou, E., Chittaganpitch, M., Chimah, O., Balmaseda, A., Buchy, P., Harris, E., Evans, V., Katayose, M., Gaur, B., O'Callaghan-Gordo, C., Goswami, D., Arvelo, W., Venter, M., Briese, T., Tokarz, R., Widdowson, M.A., Mounts, A.W., Breiman, R.F., Feikin, D.R., Klugman, K.P., Olsen, S.J., Gessner, B.D., Wright, P.F., Rudan, I., Broor, S., Simões, E.A., Campbell, H., 2011. Global burden of respiratory infections due to seasonal influenza in young children: A systematic review and meta-analysis. Lancet 378, 1917–1930. https://doi.org/10.1016/S0140-6736(11)61051-9

Nieman, D.C., 1994. Exercise, Infection, and Immunity. Int. J. Sports Med. 15, S131–S141. https://doi.org/10.1055/s-2007-1021128

Nieman, D.C., Henson, D.A., Austin, M.D., Sha, W., 2011. Upper respiratory tract infection is reduced in physically fit and active adults. Br. J. Sports Med. 45, 987–992.

https://doi.org/10.1136/bjsm.2010.077875

Nieman, D.C., Nehlsen-Cannarella, S.L., Markoff, P.A., Balk-Lamberton, A.J., Yang, H., Chritton, D.B.W., Lee, J.W., Arabatzis, K., 1990. The effects of moderate exercise training on natural killer cells and acute upper respiratory tract infections. Int. J. Sports Med. 11, 467–473. https://doi.org/10.1055/s-2007-1024839

Opp, M.R., Krueger, J.M., 2015. Sleep and immunity: A growing field with clinical impact. Brain. Behav. Immun. 47, 1–3. https://doi.org/10.1016/j.bbi.2015.03.011

Paulsen, J., Mehl, A., Dewan, A., Solliga, E., Dama, J.K., Asvold, B., 2017. Associations of obesity and lifestyle with the risk and mortality of bloodstream infection in a general population : a 15-year follow-up of 64 027 individuals in the HUNT Study. Int. J. Epidemiol. 46, 1573–1581. https://doi.org/10.1093/ije/dyx091

Perreault, K., Bauman, A., Johnson, N., Britton, A., Rangul, V., Stamatakis, E., 2017. Does physical activity moderate the association between alcohol drinking and all-cause, cancer and cardiovascular diseases mortality? A pooled analysis of eight British population cohorts. Br. J. Sports Med. 51, 651–657. https://doi.org/10.1136/bjsports-2016-096194

Prather, A.A., Leung, C.W., 2016. Association of insufficient sleep with respiratory infection among adults in the United States. JAMA Intern. Med. 176, 850–852. https://doi.org/10.1001/jamainternmed.2016.0787

Rehm, J., Baliunas, D., Borges, G.L.G., Graham, K., Irving, H., Kehoe, T., Parry, C.D., Patra, J., Popova, S., Poznyak, V., Roerecke, M., Room, R., Samokhvalov, A. V., Taylor, B., 2010. The relation between different dimensions of alcohol consumption and burden of disease: An overview. Addiction 105, 817–843. https://doi.org/10.1111/j.1360-0443.2010.02899.x

Rosenberg, G., Bauld, L., Hooper, L., Buykx, P., Holmes, J., Vohra, J., 2018. New national alcohol guidelines in the UK: Public awareness, understanding and behavioural intentions. J. Public Heal. (United Kingdom) 40, 549–556. https://doi.org/10.1093/pubmed/fdx126

Rudd, K.E., Johnson, S.C., Agesa, K.M., Shackelford, K.A., Tsoi, D., Kievlan, D.R., Colombara, D. V., Ikuta, K.S., Kissoon, N., Finfer, S., Fleischmann-Struzek, C., Machado, F.R., Reinhart, K.K., Rowan, K., Seymour, C.W., Watson, R.S., West, T.E., Marinho, F., Hay, S.I., Lozano, R., Lopez, A.D., Angus, D.C., Murray, C.J.L., Naghavi, M., 2020. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. Lancet 395, 200–211. https://doi.org/10.1016/S0140-6736(19)32989-7

Sallis, J.F., Adlakha, D., Oyeyemi, A., Salvo, D., 2020. An international physical activity and public health research agenda to inform coronavirus disease-2019 policies and practices. J. Sport Heal. Sci. 9, 328–334. https://doi.org/10.1016/j.jshs.2020.05.005

Samokhvalov, A. V., Irving, H.M., Rehm, J., 2010. Alcohol consumption as a risk factor for pneumonia: A systematic review and meta-analysis. Epidemiol. Infect. 138, 1789–1795. https://doi.org/10.1017/S0950268810000774

Scrimshaw, N.S., SanGiovanni, J.P., 1997. Synergism of nutrition, infection, and immunity: An overview. Am. J. Clin. Nutr. 66. https://doi.org/10.1093/ajcn/66.2.464S

Song, J.H., Thamlikitkul, V., Hsueh, P.R., 2011. Clinical and economic burden of community-acquired pneumonia amongst adults in the Asia-Pacific region. Int. J. Antimicrob. Agents 38, 108–117. https://doi.org/10.1016/j.ijantimicag.2011.02.017

Sopori, M., 2002. Effects of cigarette smoke on the immune system. Nat. Rev. Immunol. 2, 372–377.

Stamatakis, E., Rogers, K., Ding, D., Berrigan, D., Chau, J., Hamer, M., Bauman, A., 2015. All-cause mortality effects of replacing sedentary time with physical activity and sleeping using an isotemporal substitution model: A prospective study of 201,129 mid-aged and older adults. Int. J. Behav. Nutr. Phys. Act. 12. https://doi.org/10.1186/s12966-015-0280-7

Sudlow, C., Gallacher, J., Allen, N., Beral, V., Burton, P., Danesh, J., Downey, P., Elliott, P., Green, J., Landray, M., Liu, B., Matthews, P., Ong, G., Pell, J., Silman, A., Young, A., Sprosen, T., Peakman, T., Collins, R., 2015. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. PLoS Med. 12, 1–10. https://doi.org/10.1371/journal.pmed.1001779

Tacconelli, E., Sifakis, F., Harbarth, S., Schrijver, R., van Mourik, M., Voss, A., Sharland, M., Rajendran, N.B., Rodríguez-Baño, J., Bielicki, J., de Kraker, M., Gandra, S., Gastmeier, P., Gilchrist, K., Gikas, A., Gladstone, B.P., Goossens, H., Jafri, H., Kahlmeter, G., Leus, F., Luxemburger, C., Malhotra-Kumar, S., Marasca, G., McCarthy, M., Navarro, M.D., Nuñez-Nuñez, M., Oualim, A., Price, J., Robert, J., Sommer, H., von Cube, M., Vuong, C., Wiegand, I., Witschi, A.T., Wolkewitz, M., 2018. Surveillance for control of antimicrobial resistance. Lancet Infect. Dis. 18, e99–e106. https://doi.org/10.1016/S1473-3099(17)30485-1

Townsend, P., Phillimore, P., Beattie, A., 1988. Health and deprivation: inequality and the North. Routledge.

UK Biobank, 2007. UK Biobank: Protocol for a large-scale prospective epidemiological resource. UKBB-PROT-09-06 (Main Phase).

Wang, H.E., Baddley, J., Griffin, R.L., Judd, S., Howard, G., Donnelly, J.P., Safford, M.M., 2014. Physical inactivity and long-term rates of community-acquired sepsis. Prev. Med.

(Baltim). 65, 58–64. https://doi.org/10.1016/j.ypmed.2014.04.017

Wang, S., Liu, X., Chen, Q., Liu, C., Huang, C., Fang, X., 2017. The role of increased body mass index in outcomes of sepsis: A systematic review and meta-analysis. BMC Anesthesiol. 17, 1–11. https://doi.org/10.1186/s12871-017-0405-4

Welte, T., Torres, A., Nathwani, D., 2012. Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax 67, 71–79. https://doi.org/10.1136/thx.2009.129502

Weycker, D., Strutton, D., Edelsberg, J., Sato, R., Jackson, L.A., 2010. Clinical and economic burden of pneumococcal disease in older US adults. Vaccine 28, 4955–4960. https://doi.org/10.1016/j.vaccine.2010.05.030

Xiao, Q., Keadle, S.K., Hollenbeck, A.R., Matthews, C.E., 2014. Sleep duration and total and cause-specific mortality in a large US cohort: Interrelationships with physical activity, sedentary behavior, and body mass index. Am. J. Epidemiol. 180, 997–1006. https://doi.org/10.1093/aje/kwu222

Table 1: Lifestyle risk factor categories and index score

Risk factor	Category	Definition	Index score
Physical Activity	Inactive	0 min	0
	Insufficient	1-149 min	1
	Sufficient	≥ 150 min	2
Sedentary Behaviour	High SB	> 7 hrs	0
	Mod SB	4-7 hrs	1
	Low SB	< 4 hrs	2
Sleep	Poor index	≤ 1 sleep score	0
	Moderate index	2-3 sleep score	1
	Good index	> 3 sleep score	2
Diet	Poor quality	0 diet score	0
	Moderate quality	1 diet score	1
	Good quality	2 diet score	2
*Alcohol	Ex-drinker	*	0
	Above guideline	*	1
	Never drinker	*	2
	Within guideline	*	2
Smoking	Current		0
	Previous		1
	Never		2

*In the United Kindom, 1 unit = 8g of alcohol; Heavy drinker ≥14 units; To derive a combined lifestyle behaviour index score, ex-drinker and never drinkers were combined into the same category

Table 2: Study population characteristics at baseline. Values are means (SD) unless stated otherwise

	Lifestyle Behaviour Index Score						
Characteristic	**0-4**	**6**	**7**	**8**	**9**	**10**	**10-12**
Sample size (n)	29,281	33,641	54,524	75,083	84,975	80,357	110,582
Follow-up duration (years)	10.7 (2.0)	10.9 (1.8)	11.0 (1.6)	11.0 (1.5)	11.0 (1.4)	11.1 (1.4)	11.1 (1.3)
Age (years)	55.7 (8.0)	56.3 (7.9)	56.5 (8.0)	56.6 (8.0)	56.5 (8.1)	56.5 (8.1)	56.6 (8.3)
Women (%)	33.9	38.1	42.3	47.8	54.2	61.8	71.0
Physical activity, n (%)							
Inactive	18,355 (62.7)	14,267 (42.4)	17,485 (32.1)	18,280 (24.3)	15,400 (18.1)	8,859 (11.0)	2,575 (2.3)
Insufficient	7935 (27.1)	11,830 (35.2)	19,565 (35.9)	25,525 (34.0)	27,763 (32.7)	25,445 (31.7)	22,546 (20.4)
Sufficient	2991 (10.2)	7,544 (22.4)	17,474 (32.0)	31,278 (41.7)	41,812 (49.2)	46,053 (57.3)	85,461 (77.3)
Sedentary							
High	12,280 (41.9)	9,328 (27.7)	10,976 (20.1	10,513 (14.0)	7,917 (9.3)	4,778 (5.9)	1,693 (1.5)
Mod	14,857 (50.7)	19,861 (59.0)	33,738 (61.9)	46,350 (61.7)	50,083 (58.9)	43,161 (53.7)	41,879 (37.9)
Low	2,144 (7.3)	4,452 (13.2)	9,810 (18.0)	18,220 (24.3)	26,975 (31.7)	32,418 (40.3)	67,010 (60.6)
Sleep							
Poor quality (0-1)	4,223 (14.4)	2,618 (7.8)	2,702 (5.0)	2,319 (3.1)	1,614 (1.9)	831 (1.0)	213 (0.2)
Moderate quality (2-3)	19,984 (68.2)	21,595 (64.2)	32,430 (59.5)	39,146 (52.1)	37,002 (43.5)	28,627 (35.6)	22,351 (20.2)
Good quality (4-5)	5,074 (17.3)	9,428 (28.0)	19,392 (35.6)	33,618 (44.8)	46,359 (54.6)	50,899 (63.3)	88,018 (79.6)
Diet							
Poor quality	15,755 (53.8)	11,986 (35.6)	14,254 (26.1)	13,914 (18.5)	10,843 (12.8)	6,407 (8.0)	2,105 (1.9)
Moderate quality	11,110 (37.9)	15,717 (46.7)	26,137 (47.9)	34,933 (46.5)	36,892 (43.4)	32,400 (40.3)	29,704 (26.9)
Good quality	2,416 (8.3)	5,938 (17.7)	14,133 (25.9)	26,236 (34.9)	37,240 (43.8)	41,550 (51.7)	78,773 (71.2)
Alcohol*							
Ex-drinker	5,378 (18.4)	3,074 (9.1)	3,318 (6.1)	2,761 (3.7)	1,432 (1.7)	395 (0.5)	0 (0)
Above guideline	20,170 (68.9)	22,511 (66.9)	33,212 (60.9)	38,912 (51.8)	32,824 (38.6)	17,903 (22.3)	4,450 (4.0)
Non-drinker	662 (2.3)	1,116 (3.3)	2,251 (4.1)	3,565 (4.7)	4,390 (5.2)	3,981 (5.0)	3,625 (3.3)
Within guideline	3,071 (10.5)	6,940 (20.6)	15,743 (28.9)	29,845 (39.7)	46,329 (54.5)	58,078 (72.3)	102,507 (92.7)
Smoking							
Current	13,416 (45.8)	9,168 (27.3)	9,691 (17.8)	8,091 (10.8)	5,057 (6.0)	2,466 (3.1)	692 (0.6)
Previous	12,131 (41.4)	16,390 (48.7)	26,429 (48.5)	33,555 (44.7)	32,164 (37.9)	23,784 (29.6)	18,537 (16.8)

Never	3,734 (12.8)	8,083 (24.0)	18,404 (33.8)	33,437 (44.5)	47,754 (56.2)	54,107 (67.3)	91,353 (82.6)
Townsend deprivation index [median (IQR)]	-0.9 (-3.0, 2.4)	-1.7 (-3.4, 1.3)	-2.0 (-3.5, 0.9)	-2.1 (-3.6, 0.5)	-2.3 (-3.7, 0.2)	-2.4 (-3.7, 0.0)	-2.5 (-3.8, -0.3)
Body Mass Index	28.8 (5.3)	28.6 (5.1)	28.2 (4.9)	27.9 (4.8)	27.5 (4.7)	27.0 (4.6)	26.1 (4.3)
Ethnicity (%)							
White	95.8	95.9	95.5	95.2	94.8	94.5	94.9
South Asian	1.3	1.4	1.6	1.8	2.0	2.0	1.7
Black	1.3	1.2	1.4	1.4	1.4	1.6	1.6
Chinese	0.1	0.2	0.2	0.3	0.3	0.4	0.4
Other	1.5	1.4	1.3	1.3	1.4	1.5	1.4
Comorbidities (%)							
Cancer	8.2	7.9	8.3	8.1	8.3	8.4	8.5
Cardiovascular disease	38.3	35.8	33.9	31.4	29.0	27.0	23.7
Diabetes	8.0	7.0	6.1	5.4	4.8	4.1	3.1
Chronic respiratory illness	16.4	14.6	13.6	13.2	12.6	12.2	11.3
Liver disease	0.6	0.4	0.3	0.3	0.2	0.2	0.2
End-stage renal disease	0.2	0.1	0.1	0.1	<0.1	<0.1	<0.1
Immune disorders/HIV	0.5	0.4	0.4	0.4	0.4	0.3	0.3

* In the United Kingdom, 1 unit = 8g of alcohol; Heavy drinker ≥14 units; Physical activity was classified based on MET-min/week where inactive = 0 MET-min/week, insufficient < 600 MET-min/week (<150 min of mvpa), sufficient ≥ 600 MET-min/week (≥ 150 min of mvpa); Sedentary was classified as High >7 hrs, Mod ≥4 hrs;, Low <4 hrs; Sleep quality was based on five sleep characteristics which included: morning chronotype, sleep duration, insomnia, snoring, and daytime sleepiness; Diet was based on the Alternative Healthy Eating Index; Townsend deprivation index scores ranged from -6 to 11. Scores were derived from national census data. Each participant was assigned a score relative to the output area in which their postcode was located. Higher scores reflect a higher degree of socioeconomic deprivation; Body mass index = weight (kg) / height (m^2)

Table 3: Lifestyle risk factors and infectious disease mortality hazard ratio

Risk factor		N	Events	Model 1 HR (95% CI)		Model 2 HR (95% CI)	
Physical Activity	Inactive	95,221	1288	1.00	(ref)	1.00	(ref)
	Insufficient	140,609	1173	0.65	(0.60, 0.70)	0.77	(0.71, 0.83)
	Sufficient	232,613	1715	0.52	(0.48, 0.56)	0.64	(0.59, 0.69)
Sedentary Behaviour	High	57,485	748	1.00	(ref)	1.00	(ref)
	Moderate	249,929	2354	0.70	(0.65, 0.76)	0.86	(0.79, 0.93)
	Low	161,029	1074	0.60	(0.55, 0.66)	0.79	(0.72, 0.87)
Sleep							
	Poor	14,520	212	1.00	(ref)	1.00	(ref)
	Moderate	201,135	2004	0.66	(0.57, 0.76)	0.83	(0.72, 0.97)
	Good	252,788	1960	0.54	(0.47, 0.62)	0.80	(0.70, 0.92)
Diet							
	Poor	75,264	750	1.00	(ref)	1.00	(ref)
	Moderate	186,893	1668	0.82	(0.75, 0.89)	0.94	(0.87, 1.03)
	Good	206,286	1758	0.67	(0.62, 0.73)	0.85	(0.77, 0.93)
Alcohol							
	Ex-drinker	16,257	340	1.00	(ref)	1.00	(ref)
	Above guideline	169,542	1584	0.39	(0.35, 0.44)	0.53	(0.47, 0.60)
	Never drinker	19,522	211	0.55	(0.46, 0.65)	0.76	(0.64, 0.91)
	Within guideline	261,842	2041	0.40	(0.35, 0.45)	0.56	(0.50, 0.63)
Smoking							
	Current	48,581	905	1.00	(ref)	1.00	(ref)
	Previous	162,990	1814	0.42	(0.39, 0.45)	0.50	(0.46, 0.54)
	Never	256,872	1457	0.28	(0.26, 0.30)	0.37	(0.34, 0.41)

Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, socioeconomic status, ethnicity, BMI, cardiovascular disease, cancer, diabetes, hypertension, use of anti-hypertensive medication, use of corticosteroids, chronic lung/respiratory disease, liver diseases, diabetes, end-stage renal disease, and immune disorders/HIV and mutually adjusted for each lifestyle risk factor; Physical Activity = [Inactive = 0 min of moderate to vigorous physical activity (mvpa)]; Insufficient = 1-149 min of mvpa; Sufficient ≥ 150 min of mvpa; Sedentary Behaviour = [High > 7 hrs; Moderate = 4-7 hrs; Low <4 hrs]; Sleep = [Poor index ≤ 1 sleep score; Moderate index 2-3 sleep score; Good index > 3 sleep score]; Diet = [Poor quality = 0 diet score; Moderate quality = 1 diet score; Good quality = 2 diet score]. Alcohol = [Above guideline ≥14 units; 1 unit = 8 g of alcohol].

Table 4: Lifestyle risk factors and pneumonia mortality hazard ratio

Risk factor		N	Events	Model 1 HR (95% CI)		Model 2 HR (95% CI)	
Physical Activity	Inactive	95,221	984	1.00	(ref)	1.00	(ref)
	Insufficient	140,609	893	0.64	(0.59, 0.71)	0.77	(0.70, 0.84)
	Sufficient	232,613	1293	0.51	(0.47, 0.55)	0.63	(0.58, 0.69)
Sedentary Behaviour	High	57,485	583	1.00	(ref)	1.00	(ref)
	Moderate	249,929	1773	0.68	(0.62, 0.75)	0.83	(0.76, 0.92)
	Low	161,029	814	0.60	(0.53, 0.66)	0.78	(0.70, 0.87)
Sleep							
	Poor	14,520	160	1.00	(ref)	1.00	(ref)
	Moderate	201,135	1521	0.66	(0.56, 0.78)	0.83	(0.70, 0.98)
	Good	252,788	1489	0.54	(0.46, 0.63)	0.80	(0.68, 0.95)
Diet							
	Poor	75,264	584	1.00	(ref)	1.00	(ref)
	Moderate	186,893	1278	0.80	(0.73, 0.88)	0.94	(0.85, 1.03)
	Good	206,286	1308	0.64	(0.58, 0.70)	0.82	(0.75, 0.91)
Alcohol							
	Ex-drinker	16,257	261	1.00	(ref)	1.00	(ref)
	Above guideline	169,542	1240	0.39	(0.34, 0.45)	0.54	(0.47, 0.61)
	Never drinker	19,522	156	0.53	(0.43, 0.65)	0.75	(0.61, 0.92)
	Within guideline	261,842	1513	0.38	(0.34, 0.44)	0.55	(0.48, 0.63)
Smoking							
	Current	48,581	727	1.00	(ref)	1.00	(ref)
	Previous	162,990	1393	0.39	(0.36, 0.43)	0.46	(0.42, 0.51)
	Never	256,872	1050	0.25	(0.23, 0.28)	0.33	(0.30, 0.36)

Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, socioeconomic status, ethnicity, BMI, cardiovascular disease, cancer, diabetes, hypertension, use of anti-hypertensive medication, use of corticosteroids, chronic lung/respiratory disease, liver diseases, diabetes, end-stage renal disease, and immune disorders/HIV and mutually adjusted for each lifestyle risk factor; Physical Activity = [Inactive = 0 min of moderate to vigorous physical activity (mvpa)]; Insufficient = 1-149 min of mvpa; Sufficient ≥ 150 min of mvpa; Sedentary Behaviour = [High > 7 hrs; Moderate = 4-7 hrs; Low <4 hrs]; Sleep = [Poor index ≤ 1 sleep score; Moderate index 2-3 sleep score; Good index > 3 sleep score]; Diet = [Poor quality = 0 diet score; Moderate quality = 1 diet score; Good quality = 2 diet score]. Alcohol = [Above guideline ≥14 units; 1 unit = 8 g of alcohol].

Table 5: Lifestyle risk factors and COVID-19 mortality risk ratio

Risk factor		N	Events	Model 1 RR (95% CI)		Model 2 RR (95% CI)	
Physical Activity	Inactive	95,221	112	1.00	(ref)	1.00	(ref)
	Insufficient	140,609	115	0.75	(0.58, 0.97)	0.87	(0.67, 1.14)
	Sufficient	232,613	160	0.57	(0.44, 0.72)	0.70	(0.54, 0.89)
Sedentary Behaviour	High	57,485	68	1.00	(ref)	1.00	(ref)
	Moderate	249,929	217	0.72	(0.55, 0.95)	0.90	(0.68, 1.90)
	Low	161,029	102	0.65	(0.48, 0.89)	0.87	(0.64, 1.20)
Sleep							
	Poor	14,520	17	1.00	(ref)	1.00	(ref)
	Moderate	201,135	181	0.75	(0.46, 1.24)	0.96	(0.58, 1.58)
	Good	252,788	189	0.66	(0.40, 1.08)	0.97	(0.59, 1.61)
Diet							
	Poor	75,264	62	1.00	(ref)	1.00	(ref)
	Moderate	186,893	140	0.83	(0.61, 1.12)	0.92	(0.68, 1.25)
	Good	206,286	185	0.85	(0.64, 1.14)	1.03	(0.77, 1.39)
Alcohol							
	Ex-drinker	16,257	29	1.00	(ref)	1.00	(ref)
	Above guideline	169,542	150	0.46	(0.31, 0.69)	0.62	(0.41, 0.93)
	Never drinker	19,522	25	0.79	(0.46, 1.35)	0.87	(0.50, 1.50)
	Within guideline	261,842	183	0.44	(0.30, 0.69)	0.60	(0.40, 0.89)
Smoking							
	Current	48,581	59	1.00	(ref)	1.00	(ref)
	Previous	162,990	183	0.66	(0.49, 0.89)	0.75	(0.55, 1.02)
	Never	256,872	145	0.45	(0.33, 0.61)	0.54	(0.39, 0.74)

Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, socioeconomic status, ethnicity, BMI, cardiovascular disease, cancer, diabetes, hypertension, use of anti-hypertensive medication, use of corticosteroids, chronic lung/respiratory disease, liver diseases, diabetes, end-stage renal disease, and immune disorders/HIV and mutually adjusted for each lifestyle risk factor; Physical Activity = [Inactive = 0 min of moderate to vigorous physical activity (mvpa)]; Insufficient = 1-149 min of mvpa; Sufficient ≥ 150 min of mvpa; Sedentary Behaviour = [High > 7 hrs; Moderate = 4-7 hrs; Low <4 hrs]; Sleep = [Poor index ≤ 1 sleep score; Moderate index 2-3 sleep score; Good index > 3 sleep score]; Diet = [Poor quality = 0 diet score; Moderate quality = 1 diet score; Good quality = 2 diet score]. Alcohol = [Above guideline ≥14 units; 1 unit = 8 g of alcohol].

Figure 1 caption: Healthy lifestyle index hazard ratio for infectious diseases and pneumonia mortality. Models are adjusted for age, sex, socioeconomic status, ethnicity, BMI, cardiovascular disease, cancer, diabetes, hypertension, use of anti-hypertensive medication, use of corticosteroids, chronic lung/respiratory disease, liver diseases, diabetes, end-stage renal disease, and immune disorders/HIV. The original combined lifestyle behaviour scores ranged from 0-12. This score has been re-classified as follows: scores 0 to 4 = least Healthy group; score of 5 = 6th Healthiest group; score of 6 = 5th Healthiest group; score of 7 = 4th Healthiest group; score of 8 = 3rd Healthiest group; score of 9 = 2nd Healthiest group; scores 10 to 12 = Healthiest group.

Figure 2 caption: Healthy lifestyle index risk ratio for COVID-19 mortality. Models are adjusted for age, sex, socioeconomic status, ethnicity, BMI, cardiovascular disease, cancer, diabetes, hypertension, use of anti-hypertensive medication, use of corticosteroids, chronic lung/respiratory disease, liver diseases, diabetes, end-stage renal disease, and immune disorders/HIV. The original combined lifestyle behaviour scores ranged from 0-12. This score has been re-classified as follows: scores 0 to 4 = least Healthy group; score of 5 = 6th Healthiest group; score of 6 = 5th Healthiest group; score of 7 = 4th Healthiest group; score of 8 = 3rd Healthiest group; score of 9 = 2nd Healthiest group; scores 10 to 12 = Healthiest group.

Figure 1

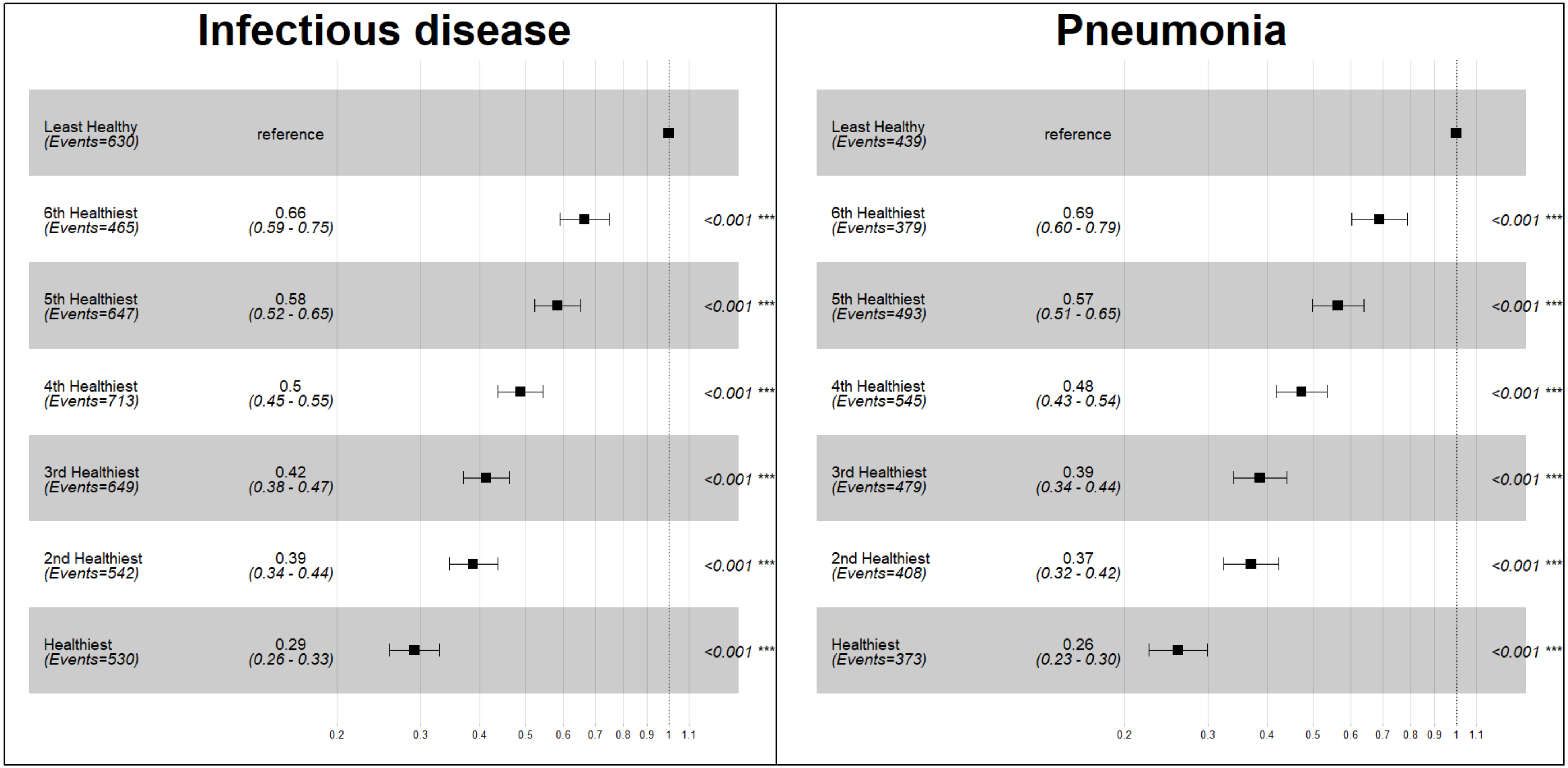
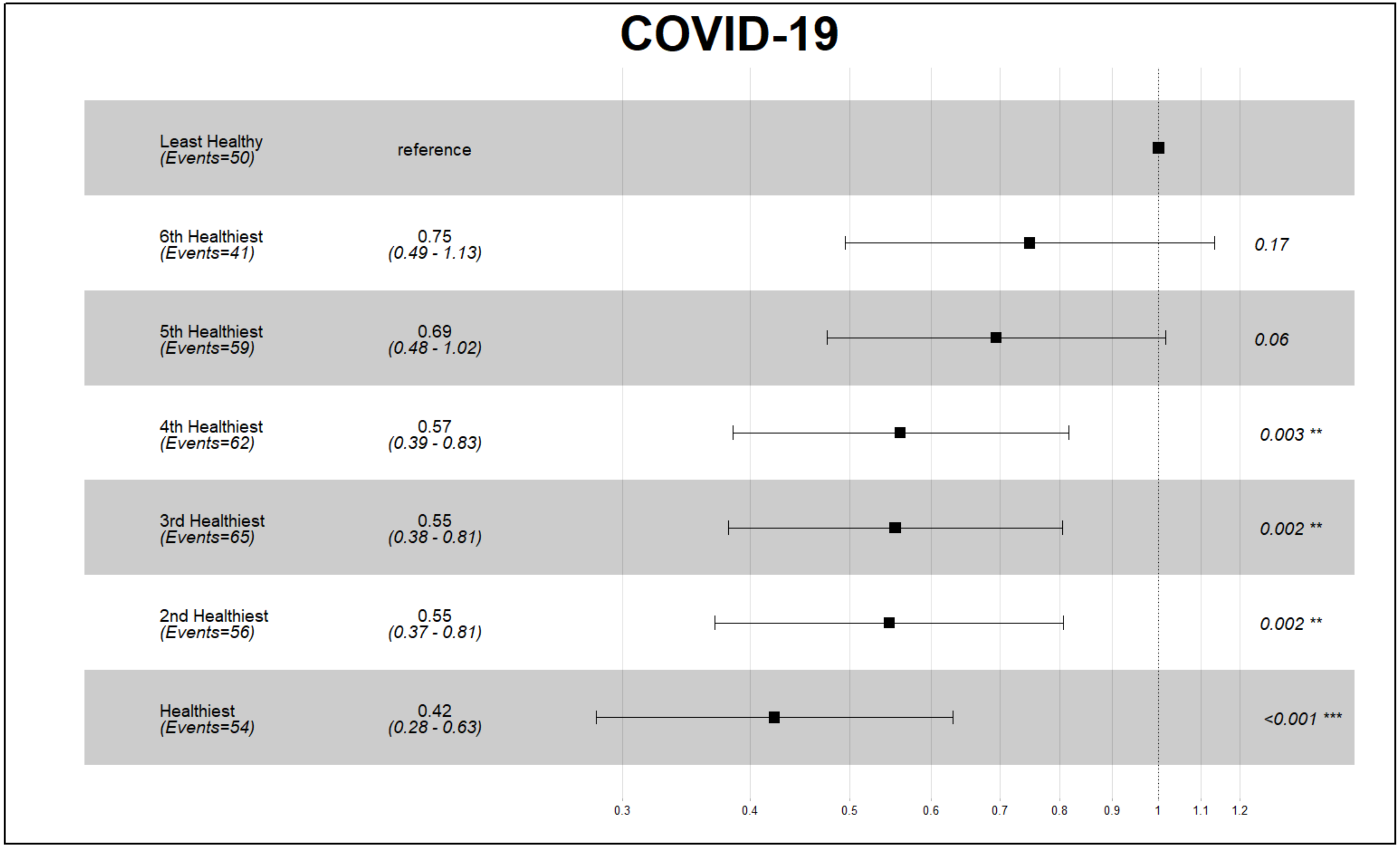

Infectious disease
Least Healthy
(Events=630)
reference
6th Healthiest
(Events=465)
0.66
(0.59 - 0.75)
<0.001 ***
5th Healthiest
(Events=647)
0.58
(0.52 - 0.65)
<0.001 ***
4th Healthiest
(Events=713)
0.5
(0.45 - 0.55)
<0.001 ***
3rd Healthiest
(Events=649)
0.42
(0.38 - 0.47)
<0.001 ***
2nd Healthiest
(Events=542)
0.39
(0.34 - 0.44)
<0.001 ***
Healthiest
(Events=530)
0.29
(0.26 - 0.33)
<0.001 ***
0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1 1.1
Pneumonia
Least Healthy
(Events=439)
reference
6th Healthiest
(Events=379)
0.69
(0.60 - 0.79)
<0.001 ***
5th Healthiest
(Events=493)
0.57
(0.51 - 0.65)
<0.001 ***
4th Healthiest
(Events=545)
0.48
(0.43 - 0.54)
<0.001 ***
3rd Healthiest
(Events=479)
0.39
(0.34 - 0.44)
<0.001 ***
2nd Healthiest
(Events=408)
0.37
(0.32 - 0.42)
<0.001 ***
Healthiest
(Events=373)
0.26
(0.23 - 0.30)
<0.001 ***
0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1 1.1

Figure 2



COVID-19
Least Healthy
(Events=50)
reference
6th Healthiest
(Events=41)
0.75
(0.49 - 1.13)
0.17
5th Healthiest
(Events=59)
0.69
(0.48 - 1.02)
0.06
4th Healthiest
(Events=62)
0.57
(0.39 - 0.83)
0.003 **
3rd Healthiest
(Events=65)
0.55
(0.38 - 0.81)
0.002 **
2nd Healthiest
(Events=56)
0.55
(0.37 - 0.81)
0.002 **
Healthiest
(Events=54)
0.42
(0.28 - 0.63)
<0.001 ***
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
1.1
1.2