

Lifestyle risk factors, obesity and infectious disease mortality in the general population: Linkage study of 97,844 adults from England and Scotland

Mark Hamer, PhD^{1,2} Gary O'Donovan, PhD³ Emmanuel Stamatakis, PhD^{2,4,5}

¹School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough LE11 3TU, United Kingdom.

²Department of Epidemiology and Public Health, University College London, London WC1E 6BT, United Kingdom.

³School of Medicine, Universidad de los Andes, Bogotá, Colombia

⁴Charles Perkins Centre Epidemiology Unit, University of Sydney, Sydney, Australia.

⁵Prevention Research Collaboration, School of Public Health, University of Sydney, Sydney, Australia.

*Correspondence: Prof Mark Hamer, Loughborough University, Loughborough LE11 3TU, United Kingdom. Phone: +44 (0) 1509 228473. Email: m.hamer@lboro.ac.uk

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Abstract

We examined associations between lifestyle variables and infectious disease mortality in a large general population cohort. A sample of 97,844 men and women (aged 47.1 ± 17.7 yrs; 46.6% male) recruited from general population, household-based surveys were followed up over mean [SD] 9.4 ± 4.5 years. Exposure measurements included self-reported physical activity, cigarette smoking, alcohol intake, and objective body mass index and waist to hip ratio. There were 9,027 deaths, of which 14.1% were attributed to infectious diseases. Compared to physically inactive participants both insufficiently active (Hazard ratio = 0.61; 95% CI, 0.50, 0.75) and sufficiently active (at least 150 min/wk moderate – vigorous activity) (0.60; 0.45, 0.78) was associated with reduced risk of infectious disease mortality in models mutually adjusted for other lifestyle factors. Ex-smokers and current smokers were at increased risk of infectious disease mortality compared with never smoker, with the strongest associations being observed for heavy smoking (>20 cigarettes/day) and pneumonia (3.30; 2.35, 4.63). Underweight was associated with increased risk of infectious disease mortality (3.65; 2.64, 5.06) compared with normal weight; the risk of viral infection was lower in overweight (0.56; 0.44, 0.72) and obesity (0.39; 0.26, 0.58). Central obesity was, however, related to higher risk of bacterial infections, but only in normal weight centrally obese participants (1.71; 1.10, 2.64). A physically active lifestyle and lifelong absence from cigarette smoking had protective associations against infectious disease mortality. Obesity has divergent associations dependent on peripheral and visceral fat depots, and the specific outcome.

Key words: Exercise; cigarette smoking; obesity; bacterial infections; virus diseases; mortality

Introduction

Infectious disease is becoming an increasing concern particularly in light of escalating microbial resistance.^{1,2} The sepsis incidence rate, for example, continues to rise³ and contributes to in excess of 5.3 million deaths per year worldwide.⁴ Sepsis deaths accounted for 7.7% of all deaths in England.⁵ Antimicrobial medications are often over-prescribed and that has led to increasing problems of antibiotic resistance. Thus, the role of lifestyle for prevention may become increasingly important in coming years. Few studies have assessed the role of multiple lifestyle factors on infection-related mortality at the population level. The majority of existing data have been from small clinical samples or case control studies,⁶ or considered individual lifestyle factors in isolation.

Previous cohort studies have mostly focused on incident pneumonia,^{7,8} pneumonia mortality,⁹ and sepsis outcomes^{10,11} and suggested possible links with physical inactivity, cigarette smoking and obesity. For example, lower levels of physical activity were associated with higher risk of community-acquired sepsis,¹⁰ and pneumonia⁷ and pneumonia mortality⁹ after accounting for other risk factors. The data on obesity, however, are inconsistent. Various studies have shown obesity to be both a risk factor⁷ and protective⁹ of pneumonia infection, and also to protect against 30-day mortality from pneumonia.^{12,13} In sepsis cases overweight, but not obesity, was associated with lower risk of mortality.⁶ Other cohort data have suggested that overweight and obesity is associated with higher risk of respiratory and skin infections,¹⁴ higher 30 day mortality risk after detection of blood borne bacterial infection,¹⁵ whilst protective against viral and fungal infections.¹⁴ The majority of obesity related infectious disease studies have focused on body mass index (BMI), but not considered central obesity both in itself and in combination with BMI.

The aim of the present study was to examine associations between multiple lifestyle risk factors, obesity (both from BMI and waist measures) and infectious disease mortality in a large general population cohort.

Materials and methods

Participants

The Health Survey for England (HSE) and the Scottish Health Survey (SHS) are household-based surveillance studies.¹⁶ Participants in the present study took part in one of the following surveys: 1994 (HSE only), 1995 (SHS only), 1997 (HSE only), 1998 (HSE and SHS), 1999 (HSE only), 2003 (HSE and SHS), 2004, 2006, 2008 (HSE only). The proportion of eligible households that took part ranged from 66% to 81%, and 91.4% of participants gave consent to prospective linkage with mortality records. A multistage, stratified probability design was used to select participants to be representative of the target populations of the corresponding countries. Stratification was based on geographical areas and not on individual characteristics: postcode (zip code) sectors were selected at the first stage and household addresses selected at the second stage. Local research ethics committees approved all aspects of each survey and all participants gave written informed consent.

Lifestyle variables

The questionnaires used to assess physical activity are described in detail elsewhere including the validity and reliability.^{17,18} In brief, trained interviewers enquired about the frequency (number of days in the last four weeks) and duration (of an average episode) of participation in: domestic physical activity; light-intensity (slow/average pace) and moderate-intensity (fairly brisk/fast pace) walking; and type-specific sports and exercises. For sports and exercises, there was a follow-up question about relative intensity: 'Was the effort of [activity] usually enough to make you out of breath or sweaty?' A compendium¹⁹ was used to identify moderate- and vigorous-intensity physical activities (MVPA) in the present study: moderate activities were of 3.0-5.9 metabolic equivalents (METs) and vigorous activities were of ≥ 6.0 METs, where one MET is considered to represent resting energy expenditure. Occupational and routine domestic activities were not included in the present analysis. As used elsewhere²⁰ participants were categorised as inactive (not reporting any MVPA),

insufficiently active ($>0 < 150$ min/week MVPA), or sufficiently active (at least 150 min/week MVPA).

Interviewers also asked about cigarette smoking and alcohol intake. Participants were first asked, 'Have you ever smoked a cigarette, a cigar or a pipe?' If participants answered yes, they were then asked, 'Do you smoke cigarettes at all nowadays?' If yes, they were asked, 'About how many cigarettes a day do you usually smoke on weekdays?' And, 'About how many cigarettes a day do you usually smoke at weekends?' Self-reported smoking has been previously validated in the present sample against objective salivary cotinine data.²¹

Participants were asked if they drank alcohol nowadays, and those who said not were categorised as 'never' drinker or 'ex-drinker' if they used to drink and had stopped. Drinkers were asked, "How often have you had an alcoholic drink of any kind during the last 12 months?"

Height and weight were measured to derive BMI, which was categorised as underweight (< 18.5 kg.m⁻²), normal weight (18.5 – 24.99 kg.m⁻²), overweight (25 – 29.99 kg.m⁻²), obese stage I (30 – 34.99 kg.m⁻²), and obese stage II (≥ 35 kg.m⁻²).²² Waist circumference was recorded twice midway between the iliac crest and lower rib and hip circumference around the widest portion of the buttocks using measuring tape. Central obesity was defined using waist to hip ratio (WHR) World Health Organization criteria (WHR ≥ 0.85 in women and WHR ≥ 0.90 in men).²³

Covariates

Age and sex were self-reported. Health status was assessed by asking participants whether they had 'any longstanding illness, disability or infirmity.' Socioeconomic status assessed using the Registrar General's classification: professional and managerial occupations; skilled, non-manual occupations; skilled manual occupations; and, routine and manual occupations.

Mortality follow-up

Participants were flagged by the British National Health Service Central Registry. For participants who survived, the data were censored up to the end of 2009 (SHS) or the first quarter of 2011 (HSE). Diagnoses for the primary cause of death were based on the International Classification of Diseases, Ninth (ICD-9) and Tenth (ICD-10) Revisions. Codes corresponding to infectious diseases were 001- 139 and 480-488 for ICD9 and A00-B99 and J09–J18 for ICD10. We further sub-typed the outcome into bacterial or viral infections, and pneumonia (as the organism was unspecified in all our cases).

Statistical analysis

Cox proportional hazards regression was used to estimate the associations of physical activity, smoking, alcohol and BMI (or WHR) with the risk of infectious disease mortality. The proportional hazards assumption was examined by comparing the cumulative hazard plots grouped on exposure, although no appreciable violations were noted. The timescale was calendar time (months). Models were adjusted for age, sex, social occupational class, longstanding illness and, where appropriate, mutually for cigarette smoking, alcohol, physical activity or BMI. Physical activity analyses were undertaken using several approaches; firstly the data were modelled using categories relevant to the current public health guidelines²⁴ in order to optimise the relevance of our results for policy makers; second, we used the data in a continuous format derived from total MET hours in order to examine dose-response relationships in more detail. In a sensitivity analysis, we excluded those who died during the first 24 months of follow-up and those reporting limiting long standing illnesses to explore possible effects of reverse causation. We conducted analyses stratified by the median length of follow up (10.7 yrs; surveys before year 2000 and later survey years 2000 onwards) to examine possible measurement dilution bias in surveys less proximal to the outcome. We also examined combinations of BMI/WHR in relation to infectious disease mortality. All analyses were performed using SPSS version 22 (IBM Inc.).

Results

The sample comprised 97,844 participants (aged 47.1 ± 17.7 yrs; 46.6% male). During 919,949 person years of follow up (mean [SD] 9.4 ± 4.5 yr; range 0 – 17 years) there were 9,027 deaths, of which 14.1% were attributed to infectious diseases. Participants dying from infectious disease were older than those dying from other causes, contained a greater proportion of ex-smokers, a higher proportion of never and ex-drinkers, were more physically inactive, reported more prevalent disease, and tended to be from lower social classes (Table 1).

Physical activity (both insufficient and sufficiently active) was associated with ~40% reduced risk of infectious disease mortality in models adjusted for all covariates (Table 2). We explored the dose-response relationship in more detailed sensitivity analyses (Table e1), which suggested there may be an “L”-shaped association between physical activity and risk of infectious disease mortality (i.e, an initial linear reduction in risk with increasing activity, followed by a flattening of the curve at higher levels). Similar patterns emerged when we examined bacterial and viral infections separately, although associations were far weaker for pneumonia mortality (Table 3).

Underweight was associated with increased risk of infectious disease mortality (hazard ratio [HR] =3.65, 95% CI, 2.64, 5.06) compared with normal weight (Table 2), and associations were consistent for both bacterial and viral outcomes, albeit strongest for pneumonia mortality (HR=4.28; 2.56, 7.15) (Table 3). Overweight and stage I obesity were associated with reduced risk of infectious disease mortality compared with normal weight (Table 2) and these associations became marginally stronger for obesity when models were adjusted for all covariates. The protective associations with overweight (HR=0.56; 0.44, 0.72) and stage I obesity (HR=0.39; 0.26, 0.58) were particularly strong for viral infections although were absent in the case of bacterial infection (Table 3). We conducted a separate analysis using participants with available data on WHR (n=68,205; events=941). There were no

associations between central obesity and all infectious disease mortality (fully adjusted HR=0.96; 0.83 – 1.10). We did, however, observe associations for bacterial infection (HR=1.41; 1.01, 1.88), but not viral (HR=0.98; 0.74, 1.30) or pneumonia mortality (HR=0.90; 0.73, 1.11). We further examined associations between combinations of BMI categories and central obesity with infectious disease mortality (Table e2) and found increased risk of bacterial infection only in normal weight centrally obese (HR=1.71; 1.10, 2.64). A reduced risk of viral infection mortality was found in all overweight and obese BMI categories regardless of central obesity.

We observed consistent associations between ex-smokers and current smokers with increased risk of infectious disease mortality compared with never smoker, although no clear dose-response pattern emerged with smoking volume (Table 2). Similar patterns of results emerged in analyses of bacterial and viral infection, although heavy smoking appeared to be a greater risk factor for viral infection (HR=2.67; 1.52, 4.11) and pneumonia (HR=3.30; 2.35, 4.63) as oppose to bacterial infections (HR=1.41; 0.87, 2.31) (Table 3). We found no associations between alcohol intake and infectious disease mortality (Table 2), albeit marginally increased risk of pneumonia in ex-drinkers (HR=1.50; 1.00, 2.24) (Table 3). In a sub-sample of participants (n=48,045; events=1058) with available data on alcohol volume (calculated by summing the units of each type of beverage and multiplying by the frequency) we did not detect any associations between hazardous or harmful drinking and infectious disease mortality (Table e3).

In sensitivity analyses we removed deaths occurring in the first 2 years of follow up but the results were not appreciably changed (Table e4). We repeated our analyses after removal of participants (n=37,557) who reported “limiting” longstanding illness (Table e5), although results were largely unchanged, albeit some associations were difficult to interpret with limited events in some groups. Although behaviours such as smoking and physical activity remain relatively stable in adulthood, body weight is more likely to fluctuate thus measurement bias is possible for exposures assessed less proximal from the outcome. Thus

we compared results from the earlier surveys (up to maximum 17 years follow up) with those from later survey years (with up to maximum of 10 years follow up). In general there were few differences (Table e6), except effect estimates for underweight were greater in the more recent surveys with shorter follow up.

Discussion

The aim of the present study was to examine associations between lifestyle risk factors and infectious disease mortality. The main findings suggest physical activity, never smoking, and overweight/obesity were protective against infectious disease mortality. There have been few community based cohort studies large enough to examine infection related mortality in the general population, and those that have specifically focused on pneumonia⁷⁻⁹ or bacterial infections.¹⁵

Previous work in population cohorts has demonstrated associations between physical activity and lower risk of community acquired pneumonia,^{7,9} sepsis,^{10,11} and 30 day mortality after detection of blood borne bacterial infection.¹⁵ A large amount of work exists on exercise and immunity²⁵ that has described a “J” shaped association between exercise and infection with optimal protection at moderate levels of activity. Nevertheless, this body of work has been traditionally based on convenience samples or elite athlete populations with soft end points such as upper respiratory tract infections.²⁶⁻²⁸ Thus, the present study adds substantially by examining associations in a large representative sample with a full spectrum of activity levels and hard endpoint. We did not find the “J” or “U” shaped associations described previously, instead we observed an “L”-shaped pattern, although infectious disease events were limited in the very highly active. The protective associations were seen even at very low levels of activity far below the current guidelines (i.e., between 1 – 3 MET-hr-wk, equivalent to moderate intensity walking for 30 min per week). Our results are highly congruent with the new 2018 US physical activity guidelines that place increased emphasis

on physical activity of any intensity and recognise the health benefits of doses below the recommended levels.²⁹

Plausible biological mechanisms exist explaining the immunological benefits of exercise,²⁵ for example, we previously observed inverse associations between physical activity and circulating inflammatory markers in the present cohort.³⁰ A body of evidence also suggests that exposure to either acute or chronic exercise significantly augments the immune response to vaccination.³¹

The existing evidence on obesity and infection are equivocal, although data from large cohort studies with substantial follow up has been lacking. Recent studies,^{9,14,15} notable for their large sample sizes and robust outcomes, all demonstrated increased risk of infection in the underweight that is consistent with our data. Inoue et al.⁹ showed that BMI above 25 kg.m⁻² was protective against pneumonia mortality; Harpsøe et al.¹⁴ suggested that overweight and obesity was associated with higher risk of respiratory and skin infections whilst protective against viral and fungal infections; Paulsen et al.¹⁵ showed that all levels of BMI defined obesity were associated with higher 30 day mortality risk after detection of blood borne bacterial infection. Thus, our results are largely consistent with these findings suggesting reduced risk of viral infection and pneumonia mortality in overweight/obese when defined from BMI. There are presently limited data on central obesity; recent evidence showed central obesity to be associated with a 1.7-fold increased risk of sepsis mortality.¹¹ We extended these findings by examining the combination of BMI (peripheral obesity) and central obesity, and showed central obesity was associated with increased risk of bacterial infection, particularly in the normal weight centrally obese. The mechanisms behind the obesity paradox are poorly understood, but there may be several explanations. Firstly, infections are often acute illnesses and nutritional reserve provided by excess adiposity may aid survival during a life-threatening period.³² We generally observed protective associations with BMI but not WHR, and although it is known that peripheral and visceral fat depots differ in morphology and function³³ little is known about specific effects on immunity. Second,

obese participants may have greater contact with primary care, and some data suggest greater use of antibiotics in this group,³⁴ which would help treat and diagnose infections more quickly avoiding more serious outcomes such as hospitalisation and death. We did not capture infections treated outside hospital settings thus were unable to explore this issue in more depth. Lastly, there remains the possibility of reverse causation whereby initially obese participants who contract infections lose weight and effectively contaminate the normal weight referent category.³⁵ Although our results were unchanged in sensitivity analysis that removed early deaths, we did not have weight histories to properly examine this issue.

Our data showed that heavy smoking was a particularly strong risk factor for pneumonia, which is consistent with increasing recognition of smoking-related lung diseases other than lung cancer and chronic obstructive pulmonary disease.^{36,37} We also observed increased risks of all types of infections in ex-smokers suggesting that tobacco may have long lasting effects. The mechanisms have been largely connected to the inflammatory effects of tobacco smoke³⁶ although remain incompletely understood. We found no associations between alcohol consumption and risk of infectious disease that replicates other findings.¹⁵ The effects of lifestyle risk factors on infection risk may also operate through intermediate disease pathways, such as diabetes and cardiovascular disease, which are associated with both poor lifestyle and increased risk of infections.^{38,39} That the associations between underweight and infection became stronger in surveys more proximal to the outcome suggests a role of underlying diseases that may contribute to both weight loss and increased risk of infections.

The key strengths of this study include the inclusion of a large population sample, validated exposure measures (including objective assessment of obesity), and the ability to examine mortality attributed to both bacterial and viral infections. The main limitation was that we were unable to objectively verify specific infections through positive blood culture and ICD codes are often limited regarding the specific organisms. Nevertheless, the overall proportion of the sample dying from bacterial infection (~0.4%) in our study was similar to

other European data that was verified through blood cultures.¹⁵ The absence of data on non-mortality related infection is a limitation of the study and our outcome likely reflects the most severe cases. Nevertheless, similar trends have been observed for non-mortality related infection⁷ and infections resulting in death⁹ relative to lifestyle risk factors. Other limitations include the possibility of residual confounding as we lacked complete data on other lifestyle variables (e.g., sedentary behaviour, diet). Physical activity was self-reported thus subject to recall bias, and did not include detailed questions on occupational activity. BMI has been criticised as a measure of obesity. Nevertheless, BMI remains a robust predictor of major causes of death in large scale population studies⁴⁰ and is a useful tool for detecting targeted metabolic traits when compared to direct measures of fat mass (such as Dual-energy X-ray absorptiometry).⁴¹

In summary, we observed associations between various lifestyle risk factors and infectious disease mortality in a large general population cohort. In light of escalating microbial resistance, healthy lifestyles should be promoted to improve resilience against infectious diseases. These findings will be important to inform future public health policy and assist physicians in clinical decisions to help improve resilience to infection.

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Table 1. Baseline characteristics according to death status

<i>Variable at baseline</i>	<i>Alive</i>	<i>Death from other causes</i>	<i>Death from infectious disease</i>
N	88817	7753	1274
Age (yrs, SD)	44.9± 16.1	66.9± 13.1	73.0± 10.9
Sex (% men)	46.1	52.3	51.1
Cigarette Smoking (%)			
Never	49.4	31.9	31.8
Ex-smoker	23.7	38.8	45.2
Light, <10/d	7.5	5.8	7.7
Medium, 10-19/d	11.0	11.0	8.1
Heavy, ≥20/d	8.5	12.4	7.2
Alcohol, frequency (%)			
Never	6.3	6.6	9.3
Ex-drinker	3.5	8.1	9.2
< monthly	13.6	17.5	19.2
1 – 2 / month	13.2	10.5	9.5
1 – 4 /week	46.2	33.9	29.7
≥5 /week	17.2	23.4	23.1
Physical activity (%)			
Inactive	47.9	80.8	86.9
Insufficiently active	29.4	12.7	8.7
Sufficiently active	22.7	6.5	4.4
Body mass index category			
Underweight	0.7	1.4	3.1
Normal	39.4	34.5	38.0
Overweight	38.6	40.8	39.8
Stage I obese	15.3	17.1	14.2
Stage II obese	5.9	6.1	4.9
Longstanding illnesses (%)	41.1	67.6	72.8
Professional occupations (%)	4.9	3.1	2.1

Table 2. Lifestyle risk factors and infectious disease mortality (N=97,844)

Risk factor	N	Deaths	Model 1 Hazard Ratio (95% CI)	Model 2 Hazard Ratio (95% CI)
<i>Physical activity</i>				
Inactive	49,960	1107	1.00 (Ref)	1.00 (Ref)
Insufficient	27,207	107	0.54 (0.34, 0.56)	0.61 (0.50, 0.75)
Sufficiently active	20,677	56	0.51 (0.39, 0.67)	0.60 (0.45, 0.78)
<i>Body mass index category</i>				
Underweight	805	40	4.07 (2.94, 5.62)	3.65 (2.64, 5.06)
Normal	38,193	484	1.00 (Ref)	1.00 (Ref)
Overweight	37,969	507	0.71 (0.63, 0.80)	0.72 (0.63, 0.81)
Stage I obese	15,125	181	0.72 (0.60, 0.85)	0.69 (0.58, 0.82)
Stage II obese	5,752	62	0.92 (0.70, 1.20)	0.82 (0.63, 1.07)
<i>Cigarette smoking</i>				
Never	46,713	405	1.00 (Ref)	1.0 (Ref)
Ex-smoker	24,604	576	1.46 (1.28, 1.67)	1.46 (1.28, 1.67)
Current, <10/d	7,235	98	2.57 (2.06, 3.20)	2.26 (1.81, 2.82)
Current, 10-19/d	10,720	103	2.32 (1.86, 2.89)	1.91 (1.53, 2.39)
Current, ≥20/d	8,565	92	2.96 (2.34, 3.74)	2.43 (1.91, 3.08)
<i>Alcohol frequency</i>				
Never	6,190	119	1.00 (Ref)	1.0 (Ref)
Ex-drinker	3,831	117	1.46 (1.18, 1.88)	1.24 (0.96, 1.61)
< monthly	13,614	244	0.99 (0.80, 1.23)	0.96 (0.77, 1.19)
1 – 2 / month	12,624	121	0.84 (0.65, 1.08)	0.88 (0.68, 1.14)
1 – 4 /week	43,859	378	0.86 (0.70, 1.06)	0.89 (0.72, 1.10)
≥5 /week	17,303	294	0.91 (0.73, 1.13)	0.94 (0.76, 1.19)

Model 1: adjusted for age and sex

Model 2: adjusted for age, sex, longstanding illness, social occupational status, and mutually for physical activity, BMI category, cigarette smoking, alcohol.

Table 3. Lifestyle risk factors and infectious disease mortality stratified by bacterial or viral origin.

Risk factor	Bacterial Hazard Ratio (95% CI) (369 deaths)	Viral Hazard Ratio (95% CI) (326 deaths)	Pneumonia Hazard Ratio (95% CI) (579 deaths)
<i>Physical activity</i>			
Inactive	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Insufficient	0.57 (0.39, 0.82)	0.36 (0.21, 0.60)	0.80 (0.61, 1.04)
Sufficiently active	0.46 (0.27, 0.79)	0.48 (0.26, 0.88)	0.76 (0.52, 1.11)
<i>Body mass index category</i>			
Underweight	2.34 (1.09, 5.03)	3.82 (2.30, 6.35)	4.28 (2.56, 7.15)
Normal	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Overweight	0.86 (0.68, 1.09)	0.56 (0.44, 0.72)	0.73 (0.61, 0.88)
Stage I obese	0.91 (0.67, 1.24)	0.39 (0.26, 0.58)	0.75 (0.58, 0.96)
Stage II obese	0.91 (0.56, 1.48)	0.76 (0.47, 1.23)	0.81 (0.53, 1.24)
<i>Cigarette Smoking</i>			
Never	1.00 (Ref)	1.0 (Ref)	1.0 (Ref)
Ex-smoker	1.43 (1.12, 1.82)	1.52 (1.17, 1.99)	1.45 (1.19, 1.76)
Light, <10/d	2.49 (1.68, 3.68)	2.58 (1.70, 3.93)	1.95 (1.37, 2.78)
Medium, 10-19/d	1.85 (1.24, 2.76)	2.17 (1.43, 3.29)	1.83 (1.29, 2.61)
Heavy, ≥20/d	1.41 (0.87, 2.31)	2.67 (1.51, 4.11)	3.30 (2.35, 4.63)
<i>Alcohol frequency</i>			
Never	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Ex-drinker	1.10 (0.68, 1.77)	1.11 (0.68, 1.80)	1.50 (1.00, 2.24)
< monthly	0.83 (0.55, 1.25)	0.87 (0.58, 1.31)	1.14 (0.81, 1.61)
1 – 2 / month	0.72 (0.45, 1.16)	0.68 (0.41, 1.14)	1.17 (0.80, 1.72)
1 – 4 /week	0.77 (0.52, 1.14)	0.87 (0.58, 1.29)	1.02 (0.73, 1.43)
≥5 /week	0.81 (0.54, 1.22)	0.85 (0.56, 1.28)	1.12 (0.80, 1.59)

Models adjusted for age, sex, longstanding illness, social occupational status, and mutually for physical activity, BMI category, cigarette smoking, alcohol.

Supplementary analyses

Table e1. Dose response pattern between physical activity and infectious disease mortality.

Physical activity (MET-hr-wk)	N	Deaths	Hazard Ratio (95% CI) ¹
Total (non-occupational)			
<1.6	16,533	591	1.00 (Ref)
1.6 – 9	22,265	296	0.68 (0.59, 0.79)
9.1 – 19	19,548	164	0.55 (0.46, 0.66)
19.1 – 37.5	19,847	117	0.44 (0.36, 0.54)
>37.5	19,619	105	0.55 (0.44, 0.68)
Sports & exercise			
0	51,557	1066	1.00 (Ref)
1 – 3	9,795	66	0.74 (0.58, 0.96)
3.1 – 9	12,913	71	0.64 (0.50, 0.82)
9.1 – 21	11,490	37	0.51 (0.36, 0.71)
>21	12,074	34	0.66 (0.47, 0.93)

¹Model adjusted for age, sex, longstanding illness, social occupational status, BMI category, smoking, alcohol.

Table e2. The association of combinations of BMI categories and central obesity with infectious disease mortality (N=68,205).

BMI/ WHR groups	HR (95% CI) All infections (941 events)	HR (95% CI) Bacterial infections (268 events)	HR (95% CI) Viral infections (244 events)	HR (95% CI) Pneumonia (429 events)
Normal weight, without central obesity	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Normal weight + central obesity	1.20 (0.97, 1.49)	1.71 (1.10, 2.64)	1.08 (0.73, 1.58)	1.08 (0.78, 1.48)
Overweight without central obesity	0.79 (0.63, 1.00)	1.04 (0.64, 1.69)	0.56 (0.35, 0.90)	0.83 (0.60, 1.15)
Overweight, + central obesity	0.85 (0.70, 1.02)	1.27 (0.86, 1.88)	0.68 (0.48, 0.97)	0.80 (0.59, 1.03)
Obese without central obesity	0.68 (0.49, 0.96)	0.85 (0.42, 1.71)	0.21 (0.10, 0.58)	0.97 (0.62, 1.50)
Obese, + central obesity	0.83 (0.66, 1.03)	1.42 (0.93, 2.16)	0.53 (0.34, 0.83)	0.76 (0.54, 1.07)

Models adjusted for age, sex, longstanding illness, social occupational status, physical activity, smoking, alcohol.

Underweight were excluded from these analyses.

Table e3. The association between alcohol volume and infectious disease mortality (N=48,045).

Alcohol group	HR (95% CI) All infections (1058 events)	HR (95% CI) Bacterial infections (322 events)	HR (95% CI) Viral infections (320 events)	HR (95% CI) Pneumonia (416 events)
Never	1.0 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Ex-drinker	1.23 (0.87, 1.76)	1.43 (0.76, 2.67)	1.20 (0.66, 2.19)	1.14 (0.62, 2.11)
Drinker, but not in last 7 days	0.84 (0.65, 1.07)	0.70 (0.44, 1.12)	0.87 (0.57, 1.33)	0.93 (0.62, 1.41)
Drinker, within guidelines ¹	0.77 (0.54, 1.10)	0.81 (0.42, 1.57)	0.73 (0.40, 1.36)	0.73 (0.41, 1.30)
Hazardous drinking ²	0.80 (0.53, 1.21)	0.84 (0.40, 1.76)	0.94 (0.46, 1.92)	0.64 (0.32, 1.26)
Harmful drinking ³	0.99 (0.59, 1.68)	1.37 (0.58, 3.25)	1.22 (0.49, 3.05)	0.47 (0.17, 1.34)

Models adjusted for age, sex, longstanding illness, social occupational status, physical activity, smoking, BMI.

¹Alcohol guidelines; <21 units/wk men, <14 units/wk women; ²Hazardous; 21- 49 units/wk men; 14-35 units/wk women; ³ Harmful; > 49 units/wk men; >35 units/wk women. Total weekly alcohol units were calculated by summing the units of each type of beverage and multiplying by the frequency. In the UK, one unit is eight grammes of alcohol, which roughly corresponds to a 25 ml measure of spirits or a half-pint of beer; And, a 175 mL glass of wine contains two units of alcohol.

Table e4. Lifestyle risk factors and infectious disease mortality removing early deaths in first 2 years of follow up (N=96,348)

Risk factor	N	Deaths	Hazard Ratio (95% CI)¹
<i>Physical activity</i>			
Inactive	48,794	882	1.00 (Ref)
Insufficient	27,017	92	0.63 (0.51, 0.78)
Sufficiently active	20,542	48	0.65 (0.49, 0.88)
<i>Body mass index category</i>			
Underweight	769	27	3.62 (2.44, 5.36)
Normal	37,597	376	1.00 (Ref)
Overweight	37,421	420	0.76 (0.66, 0.87)
Stage I obese	14,894	151	0.75 (0.62, 0.91)
Stage II obese	5,672	48	0.85 (0.63, 1.15)
<i>Smoking</i>			
Never	46,250	329	1.0 (Ref)
Ex-smoker	24,012	462	1.47 (1.27, 1.70)
Light, <10/d	7,122	77	2.24 (1.75, 2.88)
Medium, 10-19/d	10,550	75	1.82 (1.41, 2.36)
Heavy, ≥20/d	8,419	79	2.76 (2.13, 3.58)
<i>Alcohol frequency</i>			
Never	6,092	96	1.0 (Ref)
Ex-drinker	3,682	79	1.08 (0.80, 1.46)
< monthly	13,344	198	0.97 (0.76, 1.24)
1 – 2 / month	12,485	102	0.92 (0.69, 1.22)
1 – 4 /week	43,373	303	0.88 (0.70, 1.12)
≥5 /week	16,966	243	0.97 (0.76, 1.25)

¹**Model** adjusted for age, sex, longstanding illness, social occupational status, and mutually either for physical activity, BMI category, smoking, alcohol.

Table e5. Lifestyle risk factors and infectious disease mortality removing participants with limiting long standing illness (N=60,287)

Risk factor	N	Deaths	Hazard Ratio (95% CI)¹
<i>Physical activity</i>			
Inactive	26,450	250	1.00 (Ref)
Insufficient	18,292	35	0.67 (0.47, 0.97)
Sufficiently active	15,545	33	0.91 (0.63, 1.32)
<i>Body mass index category</i>			
Underweight	453	9	3.59 (1.80, 7.15)
Normal	24,159	131	1.00 (Ref)
Overweight	23,685	125	0.63 (0.50, 0.81)
Stage I obese	8,891	38	0.57 (0.40, 0.83)
Stage II obese	3,099	15	1.06 (0.61, 1.82)
<i>Smoking</i>			
Never	30,846	117	1.0 (Ref)
Ex-smoker	13,916	121	1.10 (0.84, 1.44)
Light, <10/d	4,624	20	1.78 (1.10, 2.87)
Medium, 10-19/d	6,390	32	2.08 (1.39, 3.12)
Heavy, ≥20/d	4,511	28	2.86 (1.85, 4.43)
<i>Alcohol frequency</i>			
Never	3,870	30	1.0 (Ref)
Ex-drinker	1,696	23	1.13 (0.65, 1.96)
< monthly	7,467	55	0.90 (0.58, 1.42)
1 – 2 / month	7,722	28	0.79 (0.47, 1.33)
1 – 4 /week	28,420	110	0.93 (0.61, 1.42)
≥5 /week	11,112	72	0.86 (0.55, 1.34)

¹**Model** adjusted for age, sex, longstanding illness, social occupational status, and mutually either for physical activity, BMI category, smoking, alcohol.

Table e6. Lifestyle risk factors and infectious disease mortality stratified by survey year (pre vs. post 2000)

Risk factor	Hazard Ratio (95% CI) Early surveys¹ (n=54,390; events=1077)	Hazard Ratio (95% CI) Later surveys² (n=43,437; events=197)
<i>Physical activity</i>		
Inactive	1.00 (Ref)	1.00 (Ref)
Insufficient	0.64 (0.52, 0.80)	0.54 (0.31, 0.94)
Sufficiently active	0.63 (0.47, 0.85)	0.57 (0.28, 1.18)
<i>Body mass index category</i>		
Underweight	3.13 (2.14, 4.58)	5.75 (2.99, 11.04)
Normal	1.00 (Ref)	1.00 (Ref)
Overweight	0.75 (0.65, 0.86)	0.67 (0.48, 0.93)
Stage I obese	0.74 (0.61, 0.89)	0.61 (0.40, 0.95)
Stage II obese	0.97 (0.72, 1.30)	0.61 (0.31, 1.19)
<i>Smoking</i>		
Never	1.00 (Ref)	1.0 (Ref)
Ex-smoker	1.44 (1.24, 1.66)	1.47 (1.06, 2.04)
Light, <10/d	2.32 (1.84, 2.93)	0.96 (0.38, 2.09)
Medium, 10-19/d	1.84 (1.44, 2.34)	2.13 (1.21, 3.77)
Heavy, ≥20/d	2.29 (1.76, 2.97)	3.07 (1.69, 5.05)
<i>Alcohol frequency</i>		
Never	1.00 (Ref)	1.00 (Ref)
Ex-drinker	1.18 (0.89, 1.56)	1.85 (0.90, 3.77)
< monthly	0.91 (0.72, 1.16)	1.58 (0.85, 2.93)
1 – 2 / month	0.88 (0.67, 1.16)	1.03 (0.49, 2.15)
1 – 4 /week	0.90 (0.72, 1.13)	0.93 (0.50, 1.76)
≥5 /week	0.93 (0.74, 1.19)	1.23 (0.66, 2.32)

Model adjusted for age, sex, longstanding illness, social occupational status, and mutually either for physical activity, BMI category, smoking, alcohol.

¹Includes 1994 (HSE only), 1995 (SHS only), 1997 (HSE only), 1998 (HSE and SHS), 1999 (HSE only); ²Includes 2003 (HSE and SHS), 2004, 2006, 2008 (HSE only).