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

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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 9027 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.

1. Introduction

Infectious disease is becoming an increasing concern particularly in light of escalating microbial resistance (Wells and Piddock, 2017; Global and Public Health Group, 2017). The sepsis incidence rate, for example, continues to rise (Walkey et al., 2015) and contributes to in excess of 5.3 million deaths per year worldwide (Fleischmann et al., 2016). Sepsis deaths accounted for 7.7% of all deaths in England (McPherson et al., 2013). 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 (Wang et al., 2017), or considered individual lifestyle factors in isolation.

Previous cohort studies have mostly focused on incident pneumonia (Baik et al., 2000; Kornum et al., 2010), pneumonia mortality (Inoue et al., 2007), and sepsis outcomes (Wang et al., 2014; Williams, 2013) 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 (Wang et al., 2014), and pneumonia (Baik et al., 2000) and pneumonia mortality (Inoue et al., 2007) after accounting for other risk factors. The data on obesity, however, are inconsistent. Various studies have shown obesity to be both a risk factor (Baik et al., 2000) and protective (Inoue et al., 2007) of pneumonia infection, and also to protect against 30-day mortality from pneumonia (Corrales-Medina et al., 2011; Singanayagam et al., 2013). In sepsis cases overweight, but not obesity, was associated with lower risk of mortality (Wang et al., 2017). Other cohort data have suggested that overweight and obesity is associated with higher risk of respiratory and skin infections (Harpsoe et al.,

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2016), higher 30 day mortality risk after detection of blood borne bacterial infection (Paulsen et al., 2017), whilst protective against viral and fungal infections (Harpsoe et al., 2016). 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.

2. Materials and methods

2.1. Participants

The Health Survey for England (HSE) and the Scottish Health Survey (SHS) are household-based surveillance studies (Mindell et al., 2012). 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.

2.2. Lifestyle variables

The questionnaires used to assess physical activity are described in detail elsewhere including the validity and reliability (Stamatakis et al., 2007; Scholes et al., 2014). 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 compendium (Ainsworth et al., 2011) 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 elsewhere (O'Donovan et al., 2017) 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 (Hamer et al., 2010). 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 $kg.m^{-2}$) (World Health Organisation, 1995). 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) (World Health Organisation, 2008).

2.3. Covariates

Age and sex were self-reported. Health status was assessed by asking participants whether they had 'any longstanding illness, disability of 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.

2.4. 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).

2.5. 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 guidelines (World Health Organisation, 2010) 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.).

3. 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 9027 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).

Table 1
Baseline characteristics according to death status.

Variable at baseline	Alive	Death from other causes	Death from infectious disease
N	88,817	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

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

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)
Physical activity				
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)
Body mass index category				
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	5752	62	0.92 (0.70, 1.20)	0.82 (0.63, 1.07)
Cigarette smoking				
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	7235	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	8565	92	2.96 (2.34, 3.74)	2.43 (1.91, 3.08)
Alcohol frequency				
Never	6190	119	1.00 (ref)	1.0 (ref)
Ex-drinker	3831	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)
Physical activity			
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)
Body mass index category			
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)
Cigarette smoking			
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)
Alcohol frequency			
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.

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.

4. 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 pneumonia (Baik et al., 2000; Kornum et al., 2010; Inoue et al., 2007) or bacterial infections (Paulsen et al., 2017).

Previous work in population cohorts has demonstrated associations between physical activity and lower risk of community acquired pneumonia (Baik et al., 2000; Inoue et al., 2007), sepsis (Wang et al., 2014; Williams, 2013), and 30 day mortality after detection of blood borne bacterial infection (Paulsen et al., 2017). A large amount of work exists on exercise and immunity (Schwellnus et al., 2016) 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 (Spence et al., 2007; Matthews et al., 2002; Nieman et al., 2011). 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 and 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 (Physical Activity Guidelines Advisory Committee, 2018).

Plausible biological mechanisms exist explaining the immunological benefits of exercise (Schwellnus et al., 2016), for example, we previously observed inverse associations between physical activity and circulating inflammatory markers in the present cohort (Hamer and Stamatakis, 2009). A body of evidence also suggests that exposure to either acute or chronic exercise significantly augments the immune response to vaccination (Pascoe et al., 2014).

The existing evidence on obesity and infection are equivocal, although data from large cohort studies with substantial follow up has been lacking. Recent studies (Inoue et al., 2007; Harpsoe et al., 2016; Paulsen et al., 2017), notable for their large sample sizes and robust outcomes, all demonstrated increased risk of infection in the underweight that is consistent with our data. Inuoe et al. (Inoue et al., 2007) showed that BMI above 25 $kg.m^{-2}$ was protective against pneumonia mortality; Harpsøe et al. (Harpsoe et al., 2016) 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. (Paulsen et al., 2017) 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 (Williams, 2013). 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 (Niedziela et al., 2014). 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 function (Gesta et al., 2007) 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 (Wang and Chen, 2015), 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 (Stokes and Preston, 2016). 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 (Crotty Alexander et al., 2015; Carter et al., 2015). 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 smoke (Crotty Alexander et al., 2015) although remain incompletely understood. We found no associations between alcohol consumption and risk of infectious disease that replicates other findings (Paulsen et al., 2017). 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 (Wang et al., 2012; Rao Kondapally Seshasai et al., 2011). 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 (Paulsen et al., 2017). 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 infection (Baik et al., 2000) and infections resulting in death (Inoue et al., 2007) 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 studies (Global BMI Mortality Collaboration et al., 2016) 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) (Bell et al., 2018).

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.

Disclosures

None of the authors have any competing interests to declare.

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Contributor and guarantor information

Hamer obtained funding, conceptualized and designed the study, performed analyses, drafted the initial manuscript, and approved the final manuscript as submitted. He is the manuscript's guarantor; Stamatakis conceptualized and designed the study, provided statistical input and critical revision of the manuscript, and approved the final manuscript as submitted; O'Donovan conceptualized and designed the study, provided critical revision of the manuscript and approved the final manuscript as submitted. We affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2019.03.002.

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