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Research paper

Long working hours and risk of 50 health conditions and mortality outcomes: a multicohort study in four European countries

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SUMMARY

Background: Studies on the association between long working hours and health have captured only a narrow range of outcomes (mainly cardiometabolic diseases and depression) and no outcome-wide studies on this topic are available. To achieve wider scope of potential harm, we examined long working hours as a risk factor for a wide range of disease and mortality endpoints.

Methods: The data of this multicohort study were from two population cohorts from Finland (primary analysis, n=59 599) and nine cohorts (replication analysis, n=44 262) from Sweden, Denmark, and the UK, all part of the Individual-participant Meta-analysis in Working Populations (IPD-Work) consortium. Baseline-assessed long working hours (≥55 hours per week) were compared to standard working hours (35-40 h). Outcome measures with follow-up until age 65 years were 46 diseases that required hospital treatment or continuous pharmacotherapy, all-cause, and three cause-specific mortality endpoints, ascertained via linkage to national health and mortality registers.

Findings: 2747 (4·6%) participants in the primary cohorts and 3027 (6·8%) in the replication cohorts worked long hours. After adjustment for age, sex, and socioeconomic status, working long hours was associated with increased risk of cardiovascular death (hazard ratio 1·68; 95% confidence interval 1·08-2·61 in primary analysis and 1·52; 0·90-2·58 in replication analysis), infections (1·37; 1·13-1·67 and 1·45; 1·13-1·87), diabetes (1·18; 1·01-1·38 and 1·41; 0·98-2·02), injuries (1·22; 1·00-1·50 and 1·18; 0·98-1·18) and musculoskeletal disorders (1·15; 1·06-1·26 and 1·13; 1·00-1·27). Working long hours was not associated with all-cause mortality.

Interpretation: Follow-up of 50 health outcomes in four European countries suggests that working long hours is associated with an elevated risk of early cardiovascular death and hospital-treated infections before age

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65. Associations, albeit weak, were also observed with diabetes, musculoskeletal disorders and injuries. In these data working long hours was not related to elevated overall mortality.
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Research in context

Evidence before this study

The health hazards of overworking have attracted considerable research and policy attention. We searched PubMed for research on long working hours and health up to June 2021, using terms "long working hours" and "health", "morbidity", and "mortality". We found that the studies and meta-analyses on the association between long working hours and health capture only a narrow range of outcomes (mainly cardiometabolic diseases and depression). No outcome-wide studies on this topic were available. Although it typically represents termination of exposure to long working hours, retirement during the study follow-up has rarely been considered in existing research.

Added value of this study

To facilitate a more comprehensive evaluation of long working hours as a risk factor for ill-health, we explored links with 46 common physical and mental diseases and 4 mortality endpoints before retirement (age 65) in eleven cohorts from four European countries: Finland, Sweden, Denmark, and the United Kingdom. Increased risk was observed for 14 health outcomes in primary analysis, and findings on cardiovascular death, hospital-treated infections, diabetes, injuries, and musculoskeletal disorders were replicated in independent cohort studies. However, the population attributable fraction and magnitude of these associations were relatively modest and in most cases further attenuated when the follow-up was extended beyond age 65. In women who worked long hours at baseline, onset of disease was associated with subsequent reduction in working hours. Working long hours was not associated with all-cause mortality in women or in men.

Implications of all the available evidence

Evidence on a wide range of disease endpoints is important in evaluation of risk factors, both scientifically and for policymaking. The present outcome-wide analysis suggests that working long hours may be associated with elevated risk of early cardiovascular death and hospital-treated infections, the associations with diabetes, musculoskeletal disorders, and injuries being weaker. In this European context, long working hours seem not to be a major health risk factor at the population level, a finding which is consistent with the small population-attributable fraction estimates and lack of association with total mortality.

1. Introduction

While working for extended hours may be regarded as a virtue in the labour market, there is growing evidence of a deleterious impact on health. The most extreme although rare consequence is Karoshi (a Japanese term), referring to sudden death related to overworking [1]. In population cohort studies, a slightly increased risk of stroke among individuals working 55 hours or more per week compared to those working standard 35 to 40 hours per week has been reported [2-7]. Long working hours may also be linked with other health outcomes, such as coronary heart disease, depression and diabetes, but this evidence is inconsistent including positive results [5,8-10], null findings or positive findings in a subgroup only [2,11,12], and, in relation to depression, even indications of a protective effect [13]. Recent systematic reviews and meta-analyses have found no support for an association between long working hours and cancer [3,14].

There are at least three limitations to the current evidence on working hours and disease risk. First, while there are a number of studies on specific health outcomes, few studies have simultaneously examined a wide range of diseases to facilitate a comprehensive evaluation of the association of ill health with long working hours. Provided they are methodologically rigorous, outcome-wide approaches provide protection against selective reporting and allow direct comparison of associations with different diseases [15]. Although this approach is an increasingly popular in epidemiology [15-17], we are not aware of outcome-wide studies in the context of long working hours. Second, studies have used unrestricted follow-up that include periods when individuals are no longer exposed to the risk factor of interest, for instance owing to retirement. This may cause exposure misclassification and potentially dilute associations. Long working hours may, for example, act as a trigger for cardiovascular events in individuals with high atherosclerotic plaque burden [18], and such effects would not be observable after labour market exit. Third, although survival, as indexed by all-cause mortality is a fundamental health endpoint, very few studies have assessed its relation to long working hours [19,20].

To address these limitations, we used an outcome-wide approach to examine the association of long working hours with 46 common physical and mental health conditions and 4 mortality outcomes. To estimate exposure time more precisely, we restricted disease and mortality surveillance to age 65 which is the common age for statutory retirement. In doing so, we also explored the interconnectedness of diseases associated with long working hours by examining their temporal sequence.

2. Methods

2.1. Study design and population

This is a prospective multicohort study based on the Individual-Participant-Data Meta-analysis in Working Populations (IPD-Work) consortium dataset [21]. For primary analysis using an outcome-wide approach, we pooled individual-participant data from two Finnish prospective cohort studies: the Finnish Public Sector (FPS, N = 44 635) study and the Health and Social Support (HeSSup, N = 14 964) study. These were the two IPD-Work cohort studies with outcome-wide data available on all 50 endpoints. Replication analyses on health conditions identified from primary analysis were based on data from six cohorts: Swedish Longitudinal Occupational Survey of Health (SLOSH, N = 9081) and Work, Lipids and Fibrinogen (WOLF) studies (WOLF-Stockholm N = 5560, WOLF-Norrland N = 4471), Sweden; Danish Work Environment Cohort Study (DWECS00, N = 5467; DWECS05, N = 4978), Copenhagen Psychosocial Questionnaire (COPSOQ-I, N = 1772; COPSOQ-II, N = 3387), and Burnout, Motivation, Job Satisfaction (PUMA, N = 1834) studies, Denmark; and the Whitehall II study (N = 7512), UK. These cohorts were used in analyses where

relevant outcome data were available. Sample selection is described in **Fig. 1**, and cohort-specific response rates, ranging between 40% to 80%, are provided in Web appendices 2 and 3**.**

In all included cohort studies, working hours were assessed at baseline (1991-2008). Participants were linked to electronic health records from national health registries with the end of follow-up varying between 2009 and 2020 depending on the cohort. Each constituent study in the consortium was approved by the relevant local or national authorities/ethics committees and all participants gave informed consent to participate. Further details of cohort studies are available in Web appendices 1-3.

2.2. Classification of weekly working hours at baseline

As in prior reports [2,14,22,23], we classified working hours into categories of 'less than 35 h', '35–40 h', '41–48 h', '49–54 h', and '≥55 h/week'. The first category includes part-time workers and the second represents the reference group of full-time workers with standard working hours. The category of 41–48 h/week includes those working more than standard hours but still in accordance with the European Union Working Time Directive (2003/88/EC), which guarantees employees the right to limit average weekly working time to 48 h on average. The remaining two categories comprise people with working times more than this threshold, with the top category of 55 or more hours per week being the definition for long working hours.

2.3. Follow-up for morbidity and mortality

In the two primary studies, we ascertained morbidity due to a total of 50 health outcomes following a similar procedure as in previous IPD-Work studies (Web appendix 1) [15]. Participants were linked by their unique identification number to national registries of hospital discharge information (recorded by the National Institute for Health and Welfare) and mortality (recorded by Statistics Finland). Additional information on cancer, diabetes, psychotic disorders, epilepsy, sleep disorders, cardiovascular disease (including hypertension), chronic obstructive bronchitis, asthma, inflammatory bowel disease, liver disease, and rheumatoid arthritis was available via record linkage to the Drug Reimbursement Entitlements Register of the Social Insurance Institution of Finland. In both cohort studies, the diagnosis for incident disease was coded according to the WHO International Classification of Diseases Tenth Revision (ICD-10). We focused on incident disease, excluding those with prevalent disease at baseline from the analysis; the only exception for transient health outcomes, such as infections and injuries (for details, see Web appendix 1).

Linked records encompassed 1204 ICD-10 codes, including 46 health conditions used in this study after excluding diseases with small case numbers (<20 cases in working time category '>55 h/week') to avoid unstable findings. The four mortality outcomes included were: all-cause, cancer, cardiovascular disease, and other than cancer or cardiovascular disease-related mortality (ICD-10). List of ICD-codes for each health outcome is provided in Web appendix 1.

In the replication studies, linkage was made of participants to similar national disease and mortality registries. Replication analyses were conducted only for those health conditions that were associated with long working hours in primary analysis. The same ICD-codes were used for disease definitions, but disease ascertainment was based on electronic health records from hospitalizations and deaths only.

2.4. Covariates

Baseline covariates and potential effect modifiers were age, sex, socioeconomic status (SES, classified into low/manual work and high/non-manual work), cohort and lifestyle factors (smoking, alcohol, body mass index (BMI), and low physical activity), as defined in previous IPD-Work consortium papers. A detailed description of the baseline assessments is provided in Web appendix 2.

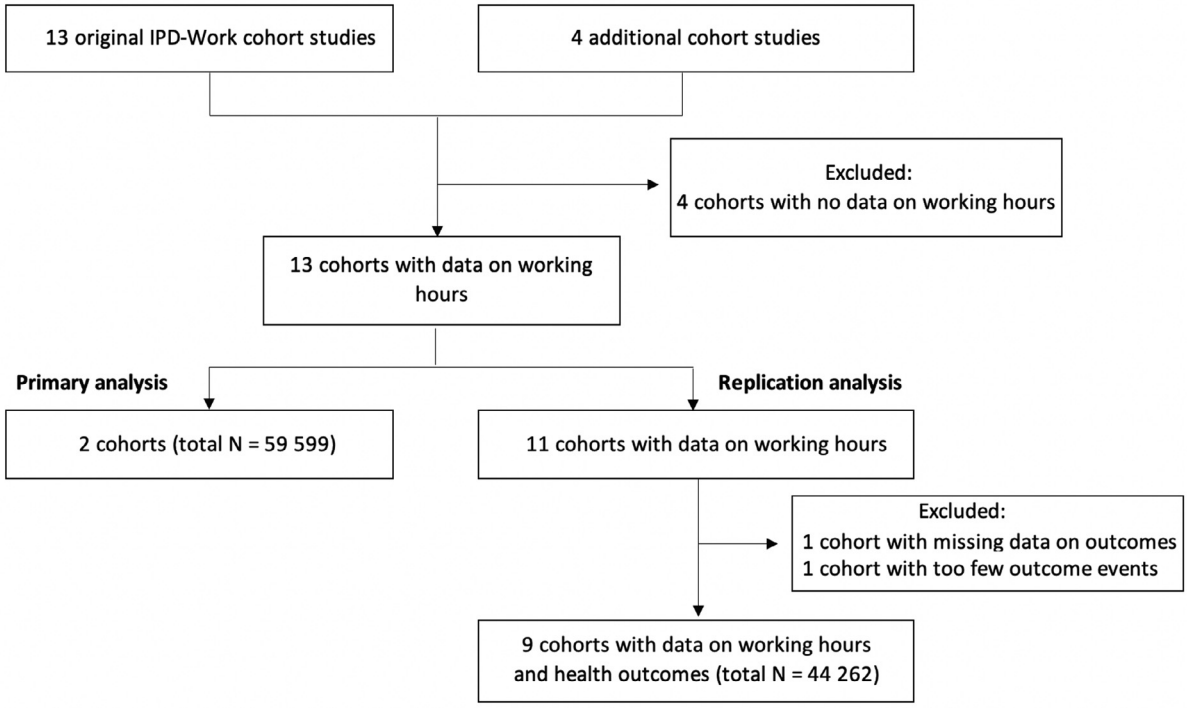

Fig. 1. Flow chat of sample selection for primary and replication analyses

2.5. Statistical analysis

In the primary analysis, we examined the associations between weekly working hours and each measure of morbidity and mortality using Cox proportional hazards regression analysis. Censoring took place at disease onset, death, end of follow-up, or age of 65, whichever occurred first. In supplementary analyses, we did not restrict the follow-up to the maximum age of 65.

Hazard ratios were adjusted for sex, age, socioeconomic status, and cohort with standard hours (35-40 h/week) as the reference. In further analyses we also took into account lifestyle factors. We also carried out stratified analyses by sex, age group (less than 50 versus 50 years or older), and socioeconomic status, testing for differences in the working hours–health outcome association according to these subgroups by computing an interaction term. To take into account multiple testing, we used false discovery rate (FDR) correction of 5% [24]. Proportionality tests with graphical illustrations are shown in Web appendix 4.

To examine the potential public health importance of long working hours as a risk factor for disease, we computed population

Table 1
Hazard ratios and 95% confidence intervals for long working hours in relation to risk of 50 outcomes.

ICD-10 disease chapter (bold) and disease endpoint	N (total)[†]	N (cases)	HR	95% CI	P for trend	Subgroup differences[‡]		
						By sex	By SES	By age
1. Infections	59154	1867	1·37*	1·13-1·67	0·009			
2. Bacterial infections	59599	1647	1·41*	1·15-1·74	0·003	0·99	0·03	0·94
3. Cancer	59065	3589	1·00	0·85-1·18	0·97			
4. Melanoma	59552	549	1·00	0·65-1·56	0·15			
5. Breast cancer	43761	1616	1·23	0·95-1·60	0·61			
6. Prostate cancer	15504	279	1·34	0·91-1·98	0·14			
7. Leukaemia, lymphoma	59538	336	1·35	0·85-2·16	0·15			
8. Endocrine diseases	59089	1864	1·25	1·04-1·50	0·36			
9. Diabetes	58995	3140	1·18	1·01-1·38	0·86	0·56	0·19	0·99
10. Mental and behavioural disorders	59268	1234	0·83	0·62-1·09	0·09			
11. Disorders due to substance abuse	59599	381	0·85	0·54-1·32	0·22			
12. Mood disorders	59439	658	0·95	0·64-1·39	0·55			
13. Diseases of the nervous system	58618	3819	1·26*	1·09-1·45	0·10			
14. Epilepsy	59205	335	1·62	1·05-2·48	0·09	0·50	0·18	0·70
15. TIA	59570	451	1·29	0·86-1·93	0·41			
16. Sleep disorders	59599	1490	1·33	1·07-1·65	0·03	0·63	0·29	0·59
17. Diseases of the eye	59205	2685	0·83	0·67-1·01	0·19			
18. Diseases of the ear	59306	733	1·10	0·78-1·55	0·66			
19. Diseases of the circulatory system	57444	6250	1·09	0·97-1·22	0·87			
20. Hypertension	55800	4388	1·01	0·88-1·16	0·04			
21. Ischemic heart diseases	59222	1588	1·12	0·91-1·38	0·71			
22. Angina pectoris	59304	715	1·28	0·95-1·72	0·70			
23. Myocardial infarction	59542	523	1·17	0·83-1·65	0·58			
24. Arrhythmias	59335	1899	1·09	0·87-1·36	0·26			
25. Cerebrovascular diseases	59521	777	1·18	0·87-1·59	0·34			
26. Stroke	59540	644	1·18	0·85-1·64	0·56			
27. Cerebral infarction	59571	408	1·36	0·93-2·00	0·22			
28. Diseases of the respiratory system	57683	4107	0·95	0·82-1·11	0·70			
29. Influenza and pneumonia	59599	1270	1·04	0·80-1·36	0·73			
30. Asthma	57522	2119	1·07	0·86-1·34	0·29			
31. Diseases of the digestive system	57466	7142	1·05	0·94-1·16	0·42			
32. Appendicitis	59599	837	1·02	0·74-1·41	0·96			
33. Diseases of liver	59599	440	1·22	0·80-1·87	0·68			
34. Diseases of the skin	59334	715	1·01	0·71-1·43	0·57			
35. Diseases of the musculoskeletal system	55669	10918	1·15*	1·06-1·26	0·56			
36. Rheumatoid arthritis and related disorders	58825	1278	1·54*	1·20-1·98	0·006	0·39	0·68	0·53
37. Osteoarthritis	59599	3633	1·08	0·92-1·27	0·82			
38. Sciatica	59599	1119	1·62*	1·28-2·05	0·002	0·09	0·50	0·46
39. Back pain	59599	476	1·25	0·83-1·87	0·29			
40. Soft tissue disorders	59599	3853	1·08	0·93-1·25	0·01			
41. Diseases of the genitourinary system	56470	7350	1·04	0·92-1·18	0·83			
42. Pregnancy complications	43116	1409	1·01	0·72-1·41	0·28			
43. Circulatory and respiratory symptoms	59599	1402	1·49*	1·21-1·84	0·004	0·39	0·51	0·17
44. Digestive and abdominal symptoms	59599	1450	1·13	0·87-1·46	0·60			
45. Injury	59599	6568	1·27*	1·14-1·41	<.0001			
46. Falls	44635	2601	1·22	1·00-1·50	0·04	0·64	0·48	0·58
47. Overall mortality	59599	1653	1·04	0·84-1·29	0·32			
48. Death, cancer	59599	810	0·78	0·54-1·14	0·20			
49. Death, cardiovascular	59599	234	1·68	1·08-2·61	0·30	0·68	0·86	0·59
50. Death, other reason	59599	609	1·05	0·75-1·47	0·35			

N, number; SES, socioeconomic status

* Statistically significant after adjustment for False Discovery Rate of 5%.

† N(total) and N(cases) consist of participants after excluding the baseline cases in question. Numbers are smaller in diseases chapters than in disease endpoints due to exclusion of baseline cases in all disease endpoints of the chapter. See eTable1 for information on diseases where baseline cases were excluded.

‡ Diseases with statistically significant ($p<0·05$) association with working ≥55 h/week. Disease chapters were omitted if specific disease(s) within the chapter had statistically significant association(s). Models are adjusted for age, sex, and SES where appropriate. For details, see eTable6–eTable8.
For clarity, significant associations are highlighted

attributable fractions (PAF) using prevalence estimates for people working long working hours and other full-time workers (35-54 h/week) and the corresponding age, sex, socioeconomic status and cohort-adjusted hazard ratios. PAF provides an estimate of the proportion of disease endpoint cases that could be avoided in the population if exposure to long working hours was completely removed assuming that the association between long working hours and health outcome is causal and is calculated as PAF = f(HR−1)/[1+f(HR−1)], in which f is the frequency of long working hours in the total population at baseline and HR is the hazard ratio for the health outcome of interest for long vs not long working hours.

To examine the generalizability of the findings from the primary analysis across geographical regions and health-care settings, we repeated analyses of statistically significant associations between long working hours and health conditions in a replication analysis based on the Swedish, Danish and UK cohorts.

To determine whether the health outcomes associated with long working hours are likely to cluster into the same individuals or be distributed across a larger group of people with different diseases, we explored the temporal sequences of ailments that were associated with long working hours in the primary and replication analyses. In separate Cox models based on the primary analysis dataset, we tested each disease pair within the group of participants who worked long hours and treated each disease both as a predictor and as an outcome of the disease pair. The follow-up started at recorded diagnosis of the predictor disease and continued until the diagnosis of the outcome disease, death, age of 65, or end of follow-up, whichever came first.

All analyses, except for meta-analysis, were done using SAS version 9·4. The code is available in Web appendix 5. Fixed effects meta-analyses were done using Stata 17 (metan package).

2.6. Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. JE, JP, STN, MJS, CL, JKS and MK had full access to all the data in the study. All authors had final responsibility for the decision to submit for publication.

3. Results

In primary analysis, 2747 of the 59,599 participants (4·6%) were categorized as working long hours (≥55 h/week). This working pattern was more than three times more common among men (9·6%) than women (2·9%) and also more prevalent in high (6·1%) relative to low (4·8%) socioeconomic groups (eTable 2).

In analyses where participants were censored at age 65, the mean duration of follow-up was 13·8 (SD=2·8) years for morbidity events and 15·3 (SD=3·5) years for mortality. As summarized in **Table 1** (details in eTable 5), long working hours were associated with a higher risk of morbidity and mortality for 14 (28%) of the 50 outcomes. Thus, after adjustment for sex, age, socioeconomic status, and cohort, hazard ratios with 95% confidence intervals for long versus standard working hours were: all infections (1·37; 1·13-1·67) including bacterial infections (1·41; 1·15-1·74); endocrine diseases (1·25; 1·04-1·50) including diabetes (1·18; 1·01-1·38); diseases of the nervous system (1·26; 1·09-1·45) including epilepsy (1·62; 1·05-2·48) and sleep disorders (1·33; 1·07-1·56); musculoskeletal diseases (1·15; 1·06-1·26) including rheumatoid arthritis and related disorders (1·54; 1·20-1·98) and sciatica (1·62; 1·28-2·05); circulatory and respiratory symptoms (1·49; 1·21-1·84); injuries (1·27; 1·14-1·41) including falls (1·22; 1·00-1·50); and cardiovascular deaths (1·68; 1·08-2·61). Except for endocrine diseases and cardiovascular deaths, all associations with disease chapters remained statistically significant after correction for multiple testing. Additional adjustment for lifestyle factors attenuated the association between long working hours and diabetes but had little effect on other health outcomes (Web appendix 6).

Evidence of a dose-response association across working time categories was observed for infections (all and bacterial), sleep disorders, rheumatoid arthritis, sciatica, circulatory and respiratory symptoms, injuries, and falls **(Fig. 2).** When we examined effect modification (interaction), there were no differences in these relationships according to sex or socioeconomic status with one exception: the association of long working hours with bacterial infections were more pronounced among participants with low (2·09; 1·49-2·93) compared to high socioeconomic status (1·12; 0·86-1·46; p for interaction < 0·03) (**Table 1**, Web appendix 6). PAFs of long working hours for the 14 health outcomes ranged between 0·7% for musculoskeletal disorders and 3·3% for cardiovascular deaths (**Table 2**).

As shown in **Fig. 3**, long working hours were not associated with all-cause mortality (1·04; 0·84-1·29 by age 65 and 1·01; 0·84-1·20 with maximum follow-up), cancer-related death (0·78; 0·54-1·14 and 0·85; 0·64-1·13) or deaths from causes other than cardiovascular disease or all cancers combined (1·05; 0·75-1·47 and 0·99; 0·74-1·32). In absolute terms, any differences in mortality outcomes between participants working long and standard hours were small. With follow-up until 65 years of age, the rate of early cardiovascular deaths was 2·5 per 10,000 person-years in participants working long hours and 1·7 per 10,000 person-years for those working regular hours. For all-cause mortality, the rates were similar in these groups. In maximum follow-up analyses, no differences in cause-specific or overall mortality between people working long and regular hours were observed. Cumulative hazards of death by age, sex and working hours confirmed that there was no separation in mortality between participants working long and standard hours (**e**Figure 2).

Replication analyses were based on 44 262 participants from nine cohorts (mean follow-up time for morbidity 8·1, and mortality 9·4 years) and showed that the following associations were reproducible with a follow-up until age 65: cardiovascular death; infections (including bacterial infections); diabetes; injuries; and musculoskeletal disorders (**Fig. 4**). The numbers in replication cohorts were insufficient for analyses of epilepsy, sleep disorders, sciatica, and rheumatoid arthritis.

We examined the temporal sequence in the onset of health outcomes associated with long working hours, including bacterial infections, diabetes, injuries, musculoskeletal disorders, and cardiovascular death (**Fig. 5**). Diabetes was related to cardiovascular death (2·87; 1·05-7·84) and bacterial infections (3·68; 2·19-6·17). Bacterial infections were related to diabetes (2·22; 1·20-4·09). In addition, there were weaker associations between diabetes and musculoskeletal disorders, between bacterial infections, musculoskeletal disorders and diabetes, and between injuries and musculoskeletal disorders (all hazard ratios < 2·0). Despite these associations, employees working long hours had only a moderately higher risk (1·27; 1·11-1·47) of multimorbidity (at least two of the following diseases: bacterial infections, diabetes, diseases of the musculoskeletal system, injury, early cardiovascular death) relative to those working standard hours (eTable 11).

Analyses with maximum follow-up were based on a mean follow-up of 15·1 (SD=1·58) years in the primary analysis and 17·3 (SD=1·75) years in the replication analysis. Hazard ratios for the associations between long hours and the 14 health outcomes were similar or lower than those in analyses restricted to age 65. Long working hours were associated with two additional health outcomes in primary analysis: prostate cancer (1·52; 1·10-2·09) and angina pectoris (1·35; 1·04-1·77). However, only the associations with infections and musculoskeletal disorders were replicated with maximum follow-up (Web appendix 7).

We performed several sensitivity and post hoc analyses. First, to address exposure misclassification due to change in working hours over time, we performed analyses using repeat data on working

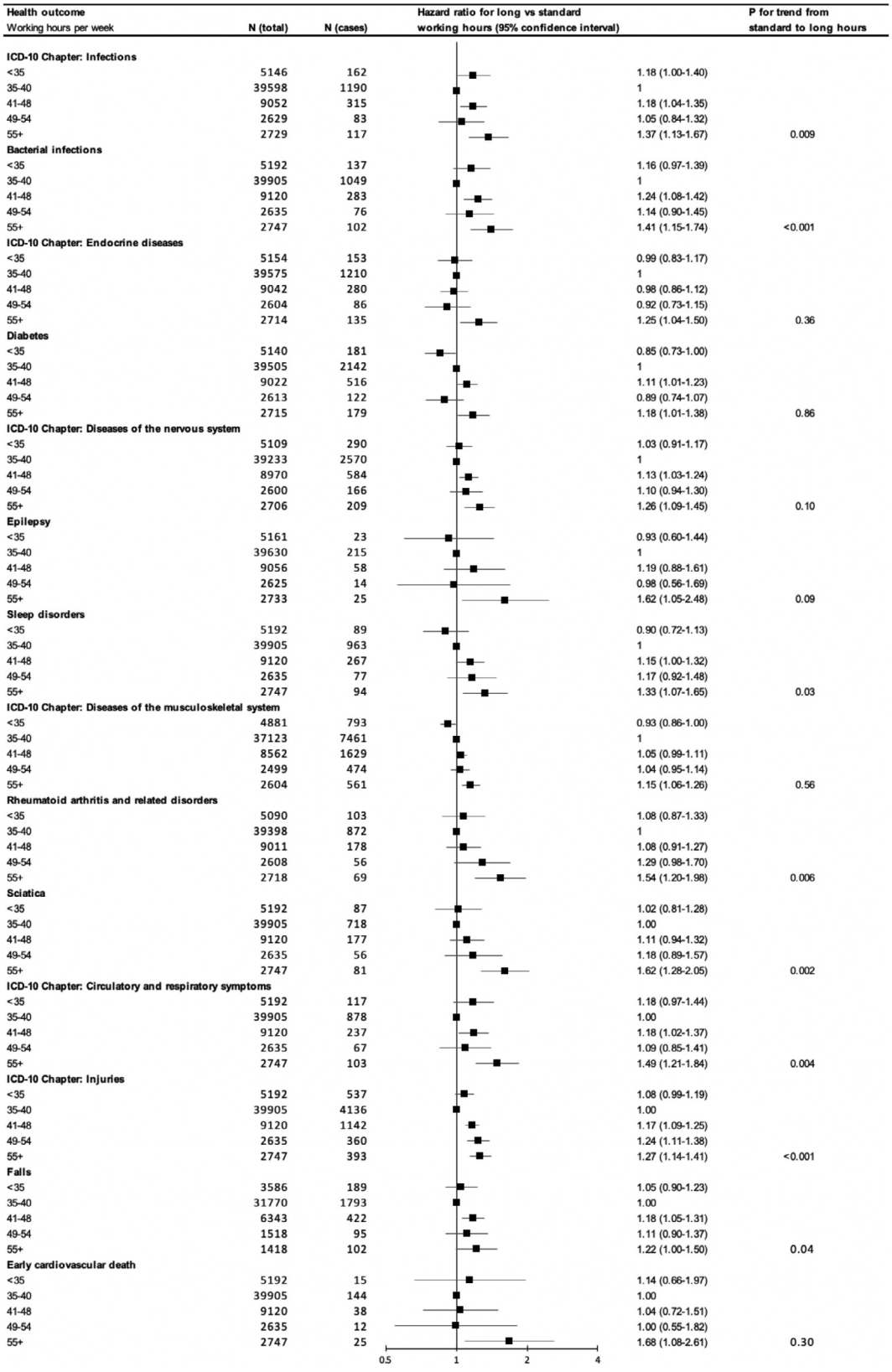

Fig. 2. Associations between categories of weekly working hours and risk of selected health outcomes until age 65 in primary analysis**Selected diseases were those with statistically significant ($p<0{\cdot}05$) association with working >55 h/week. Trends were tested across working time categories excluding part-time work. Effect estimates are adjusted for age, sex, socioeconomic status, and cohort.

Table 2
Population attributable fraction (PAF) and 95% confidence intervals for long working hours versus all other working hour categories in relation to selected outcomes*.

Disease chapter (in bold) and disease endpoints	PAF% until age 65
Infections	1·85 (0·65–3·27)
Bacterial infections	2·04 (0·73–3·61)
Endocrine diseases	1·23 (0·19–2·46)
Diabetes	0·91 (0·06–1·90)
Diseases of the nervous system	1·28 (0·44–2·24)
Epilepsy	3·01 (0·26–6·94)
Sleep disorders	1·62 (0·33–3·17)
Diseases of the musculoskeletal system	0·76 (0·28–1·29)
Rheumatoid arthritis	2·66 (0·99–4·71)
Sciatica	3·02 (1·37–5·04)
Circulatory and respiratory symptoms	2·42 (1·04–4·08)
Injuries	1·32 (0·69–2·01)
Falls	1·11 (-0·00–2·44)
Cardiovascular death	3·32 (0·40–7·52)

Hazard ratios for the calculation of PAF are adjusted for age, sex, socioeconomic status, and cohort.
* Selected diseases were those with statistically significant ($p<0·05$) association with working ≥55 h/week.

hours in two studies with repeat data on working hours. With time-dependent exposure to long working hours, the main findings were replicated although the association with diabetes did not reach statistical significance at conventional levels (eTable 12).

Second, we found little evidence of bias due to non-response. Participants working long hours were less likely to respond to a follow-up survey on working hours than those working standard hours, the relative risk for non-response being 1·36 (95% CI 1·26-1·47, eTable 13). In addition, although non-response to the survey on working hours was not associated with risk of infections, diabetes, musculoskeletal diseases and injuries (range of hazard ratios from 1·01 to 1·10), non-respondents had slightly higher rates of mortality ascribed to cardiovascular disease and all-causes (hazard ratios 1.42 and 1.34, respectively, eTable 14). Despite these differences, the findings on long working hours and health outcomes in the main analysis were replicated in a sensitivity analysis after excluding cohorts with response rate lower than 70% (eFigure 3).

Third, to explore potential reasons for associations of long working hours with increased risk of specific diseases but absence of associations with total mortality, we examined whether onset of a disease after baseline was associated with reduction in subsequent working hours among participants with long working hours at baseline. This was supported in women: the likelihood of reducing working hours was 2·00 times (95% confidence interval 1·10-3·63) higher after disease onset (eTable 15). In men with long working hours, onset of disease was not associated with subsequent reduction in working hours (hazard ratio 0·98, 95% confidence interval 0·76-1·27, p for sex difference 0·03).

4. Discussion

In this outcome-wide multicohort study, long working hours were consistently associated with a series of health events, including infections, diabetes, musculoskeletal disorders, and injuries in a working-age population. Our results also confirmed an association with death from cardiovascular disease before age 65. In total, a robust association was confirmed for six (12%) of the 50 disease endpoints studied. We found no evidence of sex differences in these associations but the association between long working hours and infectious diseases was observed only in employees with low socioeconomic status. The disease-specific population attributable fractions of 3·3% or less suggests that the burden ascribed to illness or injury associated with long working hours was modest in these European study populations. We observed no excess risk of overall mortality among people working long hours, before 65 years or with maximum follow-up.

We are not aware of other large-scale studies on long working hours and cardiovascular mortality where censoring has taken place before age 65, a common age for statutory retirement. Our findings are consistent with previous research with unrestricted follow-ups suggesting an association with stroke and a weaker association with coronary heart disease [2,4,8,22,25-27]. The association between long hours and non-fatal coronary heart disease has been previously reported in the Whitehall II study, one of the cohorts included in our replication analyses [28]. Our finding on the association before age 65 (before retirement) but not with maximum follow-up suggests that long working hours might represent an acute trigger affecting individuals with high atherosclerotic plaque burden rather than a long-term etiological risk factor for the development of coronary heart disease. This is consistent with previous research on trigger-related pathways linking long working hours to increased coagulation, atrial arrhythmia and heavy alcohol consumption [23,29,30].

The associations of long working hours with infections and musculoskeletal disorders were robust to corrections for multiple testing and the findings were replicated in independent samples and different settings. Other studies have reported a cross-sectional association between long working hours and musculoskeletal symptoms and pain [31-33]. A number of mechanisms might underlie these observations. Correlates of long working hours may contribute to these health outcomes. These include extended periods of sitting which may lead to lower back disorders including intervertebral disc and sacroiliac joint [34]. Longer working hours may also be associated with increased exposure to occupational hazards that are themselves risk factors for musculoskeletal disorders (e.g., awkward posture,

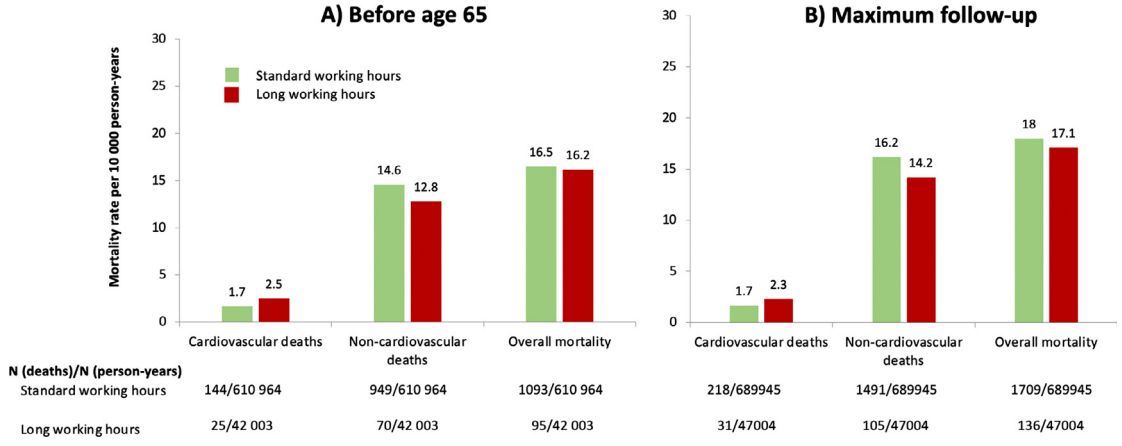

Fig. 3. Mortality rate in participants working standard and long hours in primary analysis

Health outcome Analysis	Long working hours N (total)	 N (cases)	Hazard ratio for long versus standard working hours (95% confidence interval)
All infectious diseases			
Primary analysis	2729	117	1.37 (1.13-1.67)
Replication analysis	2723	90	1.45 (1.13-1.87)
Bacterial infections			
Primary analysis	2747	102	1.41 (1.15-1.74)
Replication analysis	2391	59	1.79 (1.28-2.50)
Endocrine diseases			
Primary analysis	2714	139	1.25 (1.04-1.50)
Replication analysis	2839	144	1.03 (0.86-1.24)
Diabetes			
Primary analysis	2715	179	1.18 (1.01-1.38)
Replication analysis	2322	40	1.41 (0.98-2.02)
Diseases of the nervous system			
Primary analysis	2706	209	1.26 (1.09-1.45)
Replication analysis	2962	95	0.95 (0.77-1.19)
Diseases of the musculoskeletal system			
Primary analysis	2604	561	1.15 (1.06-1.26)
Replication analysis	2812	317	1.13 (1.00-1.27)
Circulatory and respiratory symptoms			
Primary analysis	2747	103	1.49 (1.21-1.84)
Replication analysis	3009	131	1.13 (0.93-1.37)
Injuries			
Primary analysis	2747	393	1.27 (1.14-1.41)
Replication analysis	2101	483	1.18 (0.98-1.18)
Falls			
Primary analysis	1418	102	1.22 (1.00-1.50)
Replication analysis	1957	44	0.94 (0.67-1.31)
Early cardiovascular death			
Primary analysis	2747	25	1.68 (1.08-2.61)
Replication analysis	1960	21	1.52 (0.90-2.58)

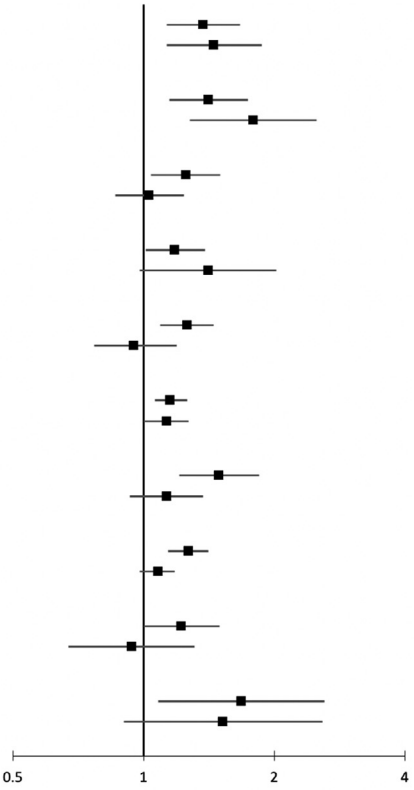

Fig. 4. Association between long working hours versus standard hours per week and selected diseases until age 65 in primary and replication analyses*
*Selected diseases were those with statistically significant ($p<0{\cdot}05$) association with long working hours. ICD-10 disease chapters instead of specific diseases are shown if the replication cohorts had less than 20 events per specific disease among participants working long hours. Models adjusted for age, sex, socioeconomic status, and cohort.

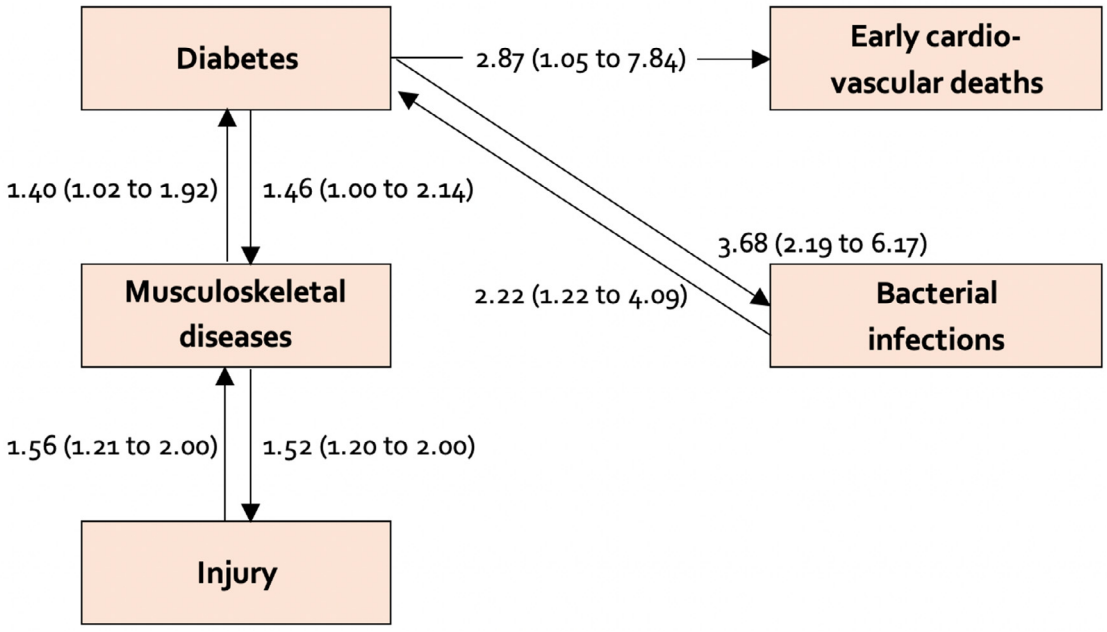

Fig. 5. Associations between disease pairs in participants who work long hours*
*Numbers are age-, sex-, socioeconomic status- and cohort-adjusted hazard ratios and their 95% confidence intervals.

twisting/rotation of the back, carrying heavy load)[35]. Increased risk of infections in relation to working long hours was confined to employees in low socioeconomic status occupations such as cleaners, practical nurses, and kitchen workers who have an increased exposure to infectious environments at work. In agreement with our findings, other studies have found a link between low socioeconomic status, psychological distress and increased risk of infectious diseases, but we are not aware of previous large-scale investigations of long working hours and infections [36-38]. Long working hours may also be associated with increased risk of psychological stress which can suppress host resistance to infections [39]. In a seminal experiment of 420 healthy subjects for who were administered either an infectious challenge (virus-containing nasal drops) or placebo (saline), psychosocial stress was associated in a dose-response manner with increased risk of subsequent respiratory illness [39].

The association between long working hours and incident diabetes was weak and, according to multivariable adjustments, largely attributable to a worse lifestyle profile (higher obesity and physical inactivity) among those working long hours. Nonetheless, the weak association with diabetes was supported by the replication analysis, and has also been reported in previous large-scale studies [2,5,11,27]. Our finding on the relationship between long working hours and increased risk of injuries is in agreement with previous studies reporting elevations in injuries, accidents, and sleep problems (a potential mediator), as potential consequences of extensive working [40-47].

In our primary analysis, long working hours were additionally associated with rheumatoid arthritis, circulatory, and respiratory symptoms, and diseases of the nervous system, such as epilepsy and sleep disorders. The associations with circulatory and respiratory symptoms or diseases of the nervous system were not replicated in independent cohort studies, suggesting that these associations may not be generalizable or robust. Case numbers were insufficient for replication analyses for rheumatoid arthritis and epilepsy. Further research is needed to examine whether these associations are reproducible. Psychosocial stress and extended periods of sitting have not been found to be associated with rheumatoid arthritis [48]. Stroke [49], infections [50], and injuries [51,52] may increase the risk of epilepsy but the association between long working hours and these factors should exceed a hazard ratio of 2.5 (i.e., be much stronger than observed here) to fully explain the 1.6-times higher incidence of epilepsy in employees with long compared to standard working hours.

Our focus on working age appears to be relevant as all PAF estimates for diseases and cause-specific mortality burden were slightly higher for the restricted follow-up than for the full follow-up extending to the post-retirement period. We found that having one disease associated with long working hours was associated with an increased risk of developing another disease associated with long hours. However, these associations were weaker than those seen in relation to some other risk factors, such as low socioeconomic position [15], and for this reason it is unsurprising that the magnitude of association of long working hours with multimorbidity was modest. These were further attenuated with age and the lack of strong associations with multimorbidity may in part explain why no excess risk of overall mortality, either before or after retirement, was observed among those working long hours. A further possible contributing factor may be the tendency to stop working long hours after onset of disease, however, this was observed only in women.

Our study was based on a large multicohort dataset and included several sensitivity, subgroup, and replication analyses to examine the robustness of the findings. We tested the observed associations in two follow-up designs: a follow-up restricted to age 65 years and maximum follow-up. The first allowed us to estimate the exposure time more precisely to years in employment before the retirement period while the latter estimated potential long-term impacts of long working hours. Other strengths of this study include the use of a wide range of morbidity and mortality endpoints which may facilitate a more comprehensive investigation into the health effects of long working hours than previous research. Further advantages of this approach compared to the traditional single exposure-single outcome design, include the opportunity to report null effects (and thus avoidance of selective publication of positive findings) [15]. However, outcome-wide approaches involve multiple testing which increases the risk of chance findings and, to offer comprehensive control for all disease-specific confounders, they require a more extensive covariate data than studies on single health outcomes. To minimise false positive findings due to multiple testing, we tested all significant associations in the primary analysis in replication analysis based on independent cohort studies from different countries. Our replication analyses also allowed investigation of the generalizability of the findings across different health care and labour market settings.

This study has several limitations. No observational study can assign causality owing to residual confounding and other biases. Selection bias due to non-response can introduce systematic error to the results, however, we found little evidence to suggest this was the case in our study. Although non-response to questionnaire survey was higher in those working long compared to standard hours and death rates were higher in non-respondents than respondents, the findings on the associations between long working hours and health outcomes remained unchanged in a sensitivity analysis excluding those cohort studies with a lower response rate. This finding is consistent with the comparison of established associations between risk factors and mortality in the UK Biobank, a study with an exceptionally low 5% response rate, against those from representative studies that have conventional response rates [53]. Despite large differences in response rates there was a close agreement for these associations between the studies.

The validity of self-reported working hours has been found to be high (Spearman correlation between self-reported and annual recorded working hours r = 0.89) [54], however, working hours inevitably fluctuates over time and this is likely to lead to an underestimation of the relationship with health outcomes. We addressed this issue in a sensitivity analysis utilising those studies with repeated assessments of working hours. The results were directionally consistent with the main findings and the effect size was broadly similar.

When assessing health outcomes, we relied on hospital discharge and death records. For some chronic conditions in primary analysis, records of entitlements of long-term medical treatments were additionally available. Use of electronic health records is not the gold standard method for diagnosis, but they provide a scalable and inexpensive solution for large cohort studies, such as ours. As this ascertainment method does not require participation in follow-up examinations, loss to follow-up is minimised. In the Whitehall II study, estimates of risk factor–cardiovascular disease associations were similar for electronic health records and repeated biomedical examinations [55]. In a subsample of UK Biobank participants, the sensitivity of hospitalisation records ranged between 78% and 91% and specificity between 84% and 85% for diagnosis of mental disorders [56]. Validity of electronic records of musculoskeletal disorders is also supported, although the studies available have mainly focused on primary care records [57-59]. However, use of electronic health records for disease ascertainment miss undiagnosed disease and, for diseases that we did not have entitlement data, milder cases who did not hospitalize during the follow-up were additionally missed. If this missingness differs between those working long and standard hours, it can introduce bias to the observed associations.

In conclusion, these findings suggest that the overall association of long working hours with adverse health outcomes in this European context might be relatively modest, a finding which is consistent with the small population attributable fraction estimates and lack of association with total mortality. To obtain a balanced view, it is important that future studies also examine the possibility that long working

hours, in particularly if not prolonged, could also be linked to some health benefits which, in part, counterbalance the adverse health effects. Further research is needed to examine, for example, the associations of longer working hours with the likelihood of promotion at work and improved job security, both considered important health resources [60], and whether the health effects of long working hours might vary depending on the reasons for such working pattern (financial pressures versus work engagement).

Author contributions

JE, MK, JP, SN and JV designed the study and generated the hypotheses. All authors participated in interpreting the data and critically reviewing the paper. JE wrote the first draft of the report. JE, MJS, CL and JKS, with help from JP, analyzed the data. All authors had access to the data presented in this paper. JE, JP, MJS, CL and JKS accessed and verified the data and take responsibility for the integrity of the dataset and the accuracy of the data analysis. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data sharing

The deidentified data for the primary analysis that support the findings of this study are available on reasonable request from the corresponding author, JE. The data are not publicly available due to legislative restrictions, as the data contains information that could compromise the privacy of the research participants. For the data used in replication analysis, data requests should be sent to MJS (UK data), CL (Swedish data), and JKS (Danish data). The statistical analysis code is available as supplementary material.

Declaration of interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work (except the research grants listed in funding); no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lanepe.2021.100212.

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