



# Severe Infection and Risk of Cardiovascular Disease: A Multicohort Study

Pyry N. Sipilä<sup>1</sup>, MD, PhD; Joni V. Lindbohm<sup>2</sup>, MD, PhD; G. David Batty<sup>3</sup>, DSc; Nelli Heikkilä<sup>4</sup>, MD, PhD; Jussi Vahtera, MD, PhD; Sakari Suominen, DMedSci; Ari Väänänen, PhD; Aki Koskinen, MSc; Solja T. Nyberg, PhD; Seppo Meri, MD, PhD; Jaana Pentti, MSc; Charlotte Warren-Gash<sup>5</sup>, PhD; Andrew C. Hayward, MD; Mika Kivimäki<sup>6</sup>, PhD

**BACKGROUND:** The excess risk of cardiovascular disease associated with a wide array of infectious diseases is unknown. We quantified the short- and long-term risk of major cardiovascular events in people with severe infection and estimated the population-attributable fraction.

**METHODS:** We analyzed data from 331 683 UK Biobank participants without cardiovascular disease at baseline (2006–2010) and replicated our main findings in an independent population from 3 prospective cohort studies comprising 271 329 community-dwelling participants from Finland (baseline 1986–2005). Cardiovascular risk factors were measured at baseline. We diagnosed infectious diseases (the exposure) and incident major cardiovascular events after infections, defined as myocardial infarction, cardiac death, or fatal or nonfatal stroke (the outcome) from linkage of participants to hospital and death registers. We computed adjusted hazard ratios (HRs) and 95% CIs for infectious diseases as short- and long-term risk factors for incident major cardiovascular events. We also calculated population-attributable fractions for long-term risk.

**RESULTS:** In the UK Biobank (mean follow-up, 11.6 years), 54 434 participants were hospitalized for an infection, and 11 649 had an incident major cardiovascular event at follow-up. Relative to participants with no record of infectious disease, those who were hospitalized experienced increased risk of major cardiovascular events, largely irrespective of the type of infection. This association was strongest during the first month after infection (HR, 7.87 [95% CI, 6.36–9.73]), but remained elevated during the entire follow-up (HR, 1.47 [95% CI, 1.40–1.54]). The findings were similar in the replication cohort (HR, 7.64 [95% CI, 5.82–10.03] during the first month; HR, 1.41 [95% CI, 1.34–1.48] during mean follow-up of 19.2 years). After controlling for traditional cardiovascular risk factors, the population-attributable fraction for severe infections and major cardiovascular events was 4.4% in the UK Biobank and 6.1% in the replication cohort.

**CONCLUSIONS:** Infections severe enough to require hospital treatment were associated with increased risks for major cardiovascular disease events immediately after hospitalization. A small excess risk was also observed in the long-term, but residual confounding cannot be excluded.

**Key Words:** cohort studies ■ communicable diseases ■ myocardial infarction ■ stroke

A series of observational studies have shown that acute respiratory and urinary tract infections, bacteremia, and sepsis are related to increased risks for myocardial infarction and stroke.<sup>1–7</sup> These findings are supported by evidence from randomized controlled trials in which influenza vaccination reduced the risk of cardiovascular events.<sup>8,9</sup> Although cardiovascular risk

appears to be highest immediately after infection, it may remain elevated for several years.<sup>1–7</sup> However, few large-scale studies have quantified the contribution of the full array of infectious disease events to the incidence of cardiovascular disease events. With infectious diseases being common, their contribution to the burden of cardiovascular disease is potentially substantial,<sup>10,11</sup> yet the

Correspondence to: Pyry Sipilä, Clinicum, Department of Public Health, PO Box 20, FI-00014 University of Helsinki, Finland. Email pyry.sipila@helsinki.fi

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## Clinical Perspective

### What Is New?

- In this multicohort study, infections severe enough to require hospital treatment were associated with a significantly increased short-term risk of major cardiovascular disease events and a slightly increased long-term risk.
- In absolute terms, the excess risk of cardiovascular events after severe infection was most marked among people with high initial cardiovascular risk.
- Between 4% and 6% of the burden of major cardiovascular events might be attributable to infections.

### What Are the Clinical Implications?

- Clinicians should be aware that people hospitalized for an infection may have an elevated short-term risk of major cardiovascular disease events.
- Cardiovascular risk estimators, such as the American College of Cardiologists/American Heart Association pooled cohort equations for 10-year atherosclerotic cardiovascular disease risk, may help identify individuals with an increased absolute risk of cardiovascular events after infection.

## Nonstandard Abbreviations and Acronyms

<b>FPS</b>	Finnish Public Sector cohort study
<b>GBD</b>	Global Burden of Disease study
<b>HeSSup</b>	Health and Social Support cohort study
<b>LDL</b>	low-density lipoprotein
<b>PAF</b>	population-attributable fraction
<b>PURE</b>	Prospective Urban Rural Epidemiology cohort study
<b>STW</b>	Still Working cohort study

proportion of cardiovascular events that could be attributable to all infections is unknown.

Several mechanisms in the acute phase of an infection may increase the short-term risk of cardiovascular events. For example, activation of inflammatory molecules and platelets, increased inflammation in atherosclerotic plaques, endothelial dysfunction, and augmented sympathetic nervous activity with catecholamine release may contribute to electrical instability of the heart, atherosclerotic plaque instability, and a concomitant hypercoagulable state.<sup>12,13</sup> Although severe infections have been linked to an increased risk of cardiovascular disease beyond the acute phase, mechanistic evidence suggests that the short-term effects of infections on the cardiovascular system are likely to be stronger than any long-term effect.<sup>14</sup>

Accordingly, we examined the short- and long-term associations between a wide range of severe infections and the occurrence of cardiovascular disease in a large cohort study alongside a replication cohort. Further, to evaluate population impact, we calculated the population-attributable fraction (PAF) for severe infections in relation to major cardiovascular events and compared this with PAFs for traditional risk factors.

## METHODS

### Transparency and Openness Promotion Statement

We provided derived variables for the administrators of the UK Biobank and Finnish cohort studies. Researchers registered with UK Biobank can apply for access to the database by completing an application, which includes a summary of the research plan, data fields required, any new data or variables that will be generated, and payment to cover the incremental costs of servicing an application (<https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access>). Pseudonymized survey data from the Finnish cohorts used in this study can be shared by investigators on request ([jenni.ervasti@ttl.fi](mailto:jenni.ervasti@ttl.fi); [sakari.suominen@utu.fi](mailto:sakari.suominen@utu.fi); [ari.vaananen@ttl.fi](mailto:ari.vaananen@ttl.fi)). Linked health records require separate permission from the Finnish Institute of Health and Welfare and Statistics Finland. In the [Supplemental Methods](#), we provide statistical codes for replicating our results so that any researcher with access to the UK Biobank and Finnish cohort studies through the procedure described can replicate our findings. The statistical codes are also available on Zenodo repository ([doi: 10.5281/zenodo.7107066](https://doi.org/10.5281/zenodo.7107066); <https://doi.org/10.5281/zenodo.7107066>).

### Primary and Replication Cohorts

We conducted analyses separately in the UK Biobank (primary cohort) and a replication cohort. The UK Biobank is a prospective cohort study in which members were enrolled from 2006 to 2010. The replication cohort consisted of harmonized and pooled individual-participant data from all 3 Finnish prospective cohort studies within the IPD-Work Consortium (Individual-Participant Data Meta-Analysis in Working Populations); eg, Finnish Public Sector (FPS), Health and Social Support (HeSSup), and Still Working (STW) studies, with study entries from 1986 to 2005.<sup>15</sup> The UK Biobank was approved by the National Health Service National Research Ethics Service (11/NW/0382), FPS by the ethics committee of the Hospital District of Helsinki and Uusimaa (HUS/1210/2016), HeSSup by the ethics committee of Turku University Hospital and the Finnish Population Register Centre (VRK 2605/410/14), and STW by the ethics committee of the Finnish Institute of Occupational Health. All participants responding to surveys or attending assessment centers gave informed consent. All participants  $\geq 18$  years of age and without cardiovascular disease at baseline were eligible for analysis. Participation rate was 5.4% in the UK Biobank and 87% in the replication cohort. A flowchart for participant selection and detailed cohort descriptions are provided in [Figures S1 and S2](#) and in the [Supplemental Methods](#).

## Exposure

In all cohorts, participants were linked to national health registries with documented validity<sup>16,17</sup> for ascertainment of exposures and outcomes from hospital discharge diagnoses. Our exposure was severe (hospital-treated) infectious diseases. We used a total of 931 codes from the *International Classification of Diseases, Tenth Revision (ICD-10)*, to capture infections that were recorded as a primary reason for a hospitalization (Table S6, for findability presented after smaller Tables S1–S5). Events classified using the eighth and ninth revisions (*ICD-8* and *ICD-9*) were converted to the *ICD-10* (Table S7). To assess the type of the infection, we considered bacterial and viral infections separately, and further classified bacterial infections to reflect major clinical entities pneumonia, gastrointestinal infections, skin infections, and urinary tract infections. We also analyzed infection severity using septic (ie, infection with life-threatening organ dysfunction<sup>18</sup>) versus nonseptic infections, which are typically less severe; infection site (lower respiratory tract, urinary tract, and gastrointestinal infections) was also analyzed, regardless of the causative pathogen.<sup>19,20</sup> Table S6 provides the *ICD-10* codes for these disease categories. For comparison purposes, we considered hospitalizations for non-infectious causes, including all hospitalizations except those that were attributable to infection, diabetes (*ICD-10* codes E10–E14) or cardiovascular disease (*ICD-10* Chapter IX) that are major risk factors for subsequent cardiovascular events, or causes that are not diseases (*ICD-10* Chapters XV, XVI, XVII, XVIII, and XXI, related to pregnancy and childbirth, perinatal period, congenital malformations, unspecific symptoms, and administration).

## Outcomes

The primary outcome was incident major cardiovascular event, comprising acute myocardial infarction, coronary heart disease death, and fatal and nonfatal stroke. Both in the UK Biobank and the replication cohort, outcome events were identified from primary diagnoses in hospital discharge records and death certificates using predefined *ICD-10* codes (I21–I22, I60–I61, and I63–I64, plus I20–I25 for coronary heart disease deaths).<sup>21,22</sup> The corresponding *ICD-9* codes were also considered, and those with existing coronary heart or cerebrovascular disease on or before baseline were excluded (Table S1). In sensitivity analyses, we complemented the outcome definition with revascularization and thrombolysis of coronary arteries and arteries supplying blood to the brain, which were available for FPS only, the largest study in the replication cohort. These records were classified according to the Finnish national edition of the *Nordic Classification of Surgical Procedures*.<sup>23</sup>

## Covariates

Covariates included major cardiovascular risk factors<sup>24</sup>: sex, socioeconomic status (low, intermediate, or high), smoking (never, former, or current), alcohol consumption (never, former, moderate, intermediate, or heavy), hypertension, diabetes, tertiles of low-density lipoprotein (LDL) cholesterol ( $\leq 3.1$ , 3.2–3.8, or  $\geq 3.9$  mmol/L), body mass index ( $< 18.5$ , 18.5–24.9, 25.0–29.9, or  $\geq 30$  kg/m<sup>2</sup>), physical activity (weekly metabolic equivalent minutes  $< 600$ , 600–3000, or  $> 3000$ ), and comorbidities that may increase the risk of infections<sup>25</sup> (chronic liver disease,

chronic kidney disease, chronic obstructive pulmonary disease, and asthma). In the replication cohort, we adjusted for sex, socioeconomic status, hypertension, and diabetes, for which we had full data. Additionally, smoking status was available for a subcohort and was used in the PAF computations. All covariates and comorbidities were measured at the start of the follow-up and were treated similarly in multivariable adjusted regression models. Socioeconomic status was measured by education (UK Biobank, FPS, and HeSSup) or occupational grade (STW). Smoking and alcohol consumption were self-reported. In the UK Biobank, hypertension was defined as blood pressure of at least 140/90 mm Hg, self-reported hypertension, or antihypertensive medication, and diabetes was defined by glycated hemoglobin  $\geq 48$  mmol/mol (6.5%), self-reported diabetes, or antidiabetic medication. For sensitivity analyses with time-updated adjustments, we retrieved additional data for hypertension (*ICD-10*: I10–I15; *ICD-9*: 401–405) and diabetes (*ICD-10*: E10–E14; *ICD-9*: 250). Body mass index was based on measured height and weight, physical activity on self-reports, and comorbidities on hospital records. LDL cholesterol was measured using a direct method. The 10-year risk of atherosclerotic cardiovascular disease was estimated using the American College of Cardiology/American Heart Association pooled cohort equations, which were based on age, sex, ethnic background, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, treatment for hypertension, current smoking status, and history of diabetes.<sup>26</sup> In the replication cohort, hypertension and diabetes mellitus were ascertained from medication reimbursements. Supplemental Methods report further details of covariate and comorbidity measurement in each cohort.

## Estimates From Published Studies

For comparison PAFs, we retrieved publicly available estimates for major cardiovascular risk factors for high-income countries from the Prospective Urban Rural Epidemiology (PURE) and Global Burden of Diseases (GBD) studies.<sup>19,24,27</sup> From the PURE study, we retrieved estimates for smoking, hypertension, high non-high-density lipoprotein cholesterol, and diabetes. From GBD, we retrieved estimates for total cardiovascular mortality (defined as the combination of mortality from ischemic heart disease and stroke) and cardiovascular mortality attributable to smoking, high systolic blood pressure, high LDL cholesterol, and high fasting plasma glucose in 2019, the most recent year available in the GBD interactive data portal (<http://ghdx.healthdata.org/gbd-results-tool>).

## Statistical Analysis

As we did previously, we modeled exposure to infections using time-dependent analysis.<sup>28</sup> Participants with an infection on or before study baseline were considered exposed from the beginning of the follow-up. Those with their first infection during the follow-up period were considered nonexposed until hospitalization for the infection and exposed thereafter. Remaining study members were considered unexposed across the entire follow-up period.

Surveillance for incident major cardiovascular events was from study entry until event occurrence, death, or end of follow-up (in the UK Biobank, March 23, 2021, in England and Scotland and February 28, 2018, in Wales; in the replication

cohort, December 31, 2016, in FPS and STW and December 31, 2012, in HeSSup), whichever came first. Because the coronavirus disease 2019 (COVID-19) pandemic could have reduced the ascertainment of cardiovascular events through reduced use of health care services by risk-averse individuals, we conducted a sensitivity analysis in which the follow-up ended on January 31, 2020 (the date before the first confirmed COVID-19 case in the United Kingdom).<sup>29</sup>

We used a Cox proportional hazards model to compute HR and 95% CI for the associations of infectious diseases with incident cardiovascular disease; scaled Schoenfeld residuals were used to test the proportionality of hazards. In the UK Biobank, we adjusted effect estimates for age, sex, socioeconomic status, smoking, alcohol consumption, hypertension, diabetes, LDL cholesterol, body mass index, physical activity, and comorbidities (chronic liver, kidney, and obstructive pulmonary disease, and asthma). To take nonproportionality of hazards into account, adjustments for sex, socioeconomic status, smoking, hypertension, and LDL cholesterol were based on stratification. In the replication cohort, we pooled individual-level data from the 3 cohort studies and took the within-study clustering of participants into account using cohort-specific baseline hazards and cohort-specific hazard estimates for covariates<sup>28</sup>; we adjusted analyses for age, sex, socioeconomic status, hypertension, and diabetes. Adjustment for age was done using age as the time scale in both the UK Biobank and the replication cohort. To control for the competing risk of death, we conducted a sensitivity analysis using the Fine–Gray model.<sup>30</sup> The competing event was defined as death from causes that did not qualify as a major cardiovascular event.

To examine the short- and longer-term associations of infections with major cardiovascular events, we computed HRs for events occurring during the first month after infection (days 1–30), events occurring after the first month but during the first year after infection (days 31–365), and events occurring >1 year after infection (ie, day 366 onward). We used time-dependent Cox models in which participants were allocated from the nonexposed to exposure group on the day of first recorded infection, and thereafter from one exposure group to another based on time since infection (for a schematic illustration, see Figure S3). We used a similar method to analyze the negative-control exposure (ie, hospitalization for noninfectious causes). Extending the main Cox model framework, we conducted further time-dependent analyses, splitting the duration of follow-up into 5 periods (0–30 days, 31–365 days, >1 year and ≤5 years, >5 and ≤10 years, and >10 years after infection) rather than the existing 3, analyzing exposure to the first versus recurrent infections, and including hypertension, diabetes, and comorbidities as time-updated covariates. In further sensitivity analyses, we compared the risk of major cardiovascular event during each follow-up period (days 1–30, 31–365, and 366 onward) after hospitalization in those hospitalized for infectious versus noninfectious causes. The follow-up commenced on the first day of hospitalization after baseline (whether for infection or for noninfection) and was used as the time scale with adjustment for age at hospitalization (40–44, 45–49, 50–54, 55–59, 60–64, 65–69, or ≥70 years). Other adjustments were as in the main analysis.

We also estimated the PAF of severe infections on major cardiovascular events. We used the HR for the entire follow-up to reflect the overall association of severe infections with the

risk of cardiovascular events. We computed the PAFs from the most adjusted estimates using a formula for adjusted HRs:

$$PAF = \frac{p\_cases(HR - 1)}{HR}$$

where  $p\_cases$  is the proportion of those with the outcome who had severe infection before the outcome and  $HR$  is adjusted HR.<sup>31</sup> We computed cardiovascular deaths attributable to infections by multiplying PAF by cardiovascular mortality estimates from the GBD. For comparison, we computed PAFs for major risk factors (smoking, high systolic blood pressure, high LDL cholesterol, and diabetes) on cardiovascular events in our cohorts using the same adjustments as with infections. We also computed PAFs from the GBD estimates as:

$$\frac{\text{Coronary heart disease mortality attributable to a risk factor} + \text{Stroke mortality attributable to a risk factor}}{\text{Total coronary heart disease mortality} + \text{Total stroke mortality}}$$

We computed the joint PAF of infections and major risk factors using the following formula:

$$PAF_{\text{joint}} = 1 - \prod_{i=1}^j (1 - PAF_i)$$

In the case of GBD estimates, we also adjusted for the mediation of risk through other risk factors using mediation factors estimated by GBD (Table S2).<sup>27</sup> We then scaled the PAF estimates for infections and major risk factors to sum up to the joint PAF.

We analyzed the data using Stata MP 16 and 17.  $P$  values were computed using  $t$  tests with unequal variances and  $\chi^2$  tests. The corresponding author had full access to all the data in the study and takes responsibility for its integrity, as well as the data analysis.

## RESULTS

In the UK Biobank, there were 331 638 participants, and in the replication cohort, there were 271 329 participants without cardiovascular disease at baseline and with information on relevant covariates. The UK Biobank participants were considerably older (mean age, 56.5 versus 34.4 years), but this was partly balanced by the longer follow-up in the replication cohort (mean, 19.2 years) versus UK Biobank (mean, 11.6 years). In Table 1, we provide further characteristics of the participants.

In the UK Biobank, 54 434 of the 331 638 participants (16%) were hospitalized for an infection before the first major cardiovascular event. Of those, 19 638 had their first infection on or before baseline, and 34 796 had their first infection during follow-up (incidence, 10.1 per 1000 person-years). The most common infections were unspecified urinary tract infection ( $n=6252$ ), unspecified gastroenteritis ( $n=3862$ ), and unspecified lobar pneumonia ( $n=3764$ ; Table S3). Of all participants, 257 368 (78%) were hospitalized for noninfectious causes. During 3 848 256 person-years at risk after baseline, 11 649

**Table 1. Characteristics of Participants of the UK Biobank and Replication Cohort (Finnish Multicohort Sample) at Study Entry**

	UK Biobank (N=331 683)	Replication cohort (N=271 329)	P for difference between cohorts
Age at entry, mean±SD, y	56.5 (8.1)	34.4 (11.4)	<0.0001
Female sex, n (%)	177 567 (53.5)	191 527 (70.6)	<0.0001
Socioeconomic status, n (%)			<0.0001
Low	45 682 (13.8)	41 183 (15.2)	
Intermediate	166 313 (50.1)	92 619 (34.1)	
High	119 688 (36.1)	137 527 (50.7)	
Smoking, n (%)			<0.0001
Never	184 693 (55.7)	70 723 (26.1)	
Former	113 731 (34.3)	26 582 (9.8)	
Current	33 259 (10.0)	25 156 (9.3)	
Data not available, n (%)*	–	148 868 (54.9)	
Hypertension, n (%)	174 766 (52.7)	8083 (3.0)	<0.0001
Diabetes, n (%)	17 013 (5.1)	2186 (0.8)	<0.0001
Low-density lipoprotein cholesterol, mean±SD, mmol/L	3.6 (0.8)	–	
Follow-up, mean±SD, y	11.6 (1.9)	19.2 (5.2)	<0.0001
Infection before or during follow-up, n (%)	54 434 (16.4)	68 945 (25.4)	<0.0001
Major cardiovascular event during follow-up, n (%)	11 649 (3.5)	9663 (3.6)	0.30
Age at major cardiovascular event, mean±SD, y	68.1 (8.1)	60.8 (11.5)	<0.0001

– indicates data not available.

\*Of 260 240 participants eligible for the largest of the 3 Finnish cohorts (Finnish public sector study), 114 835 were invited to respond to questionnaires about smoking habits.

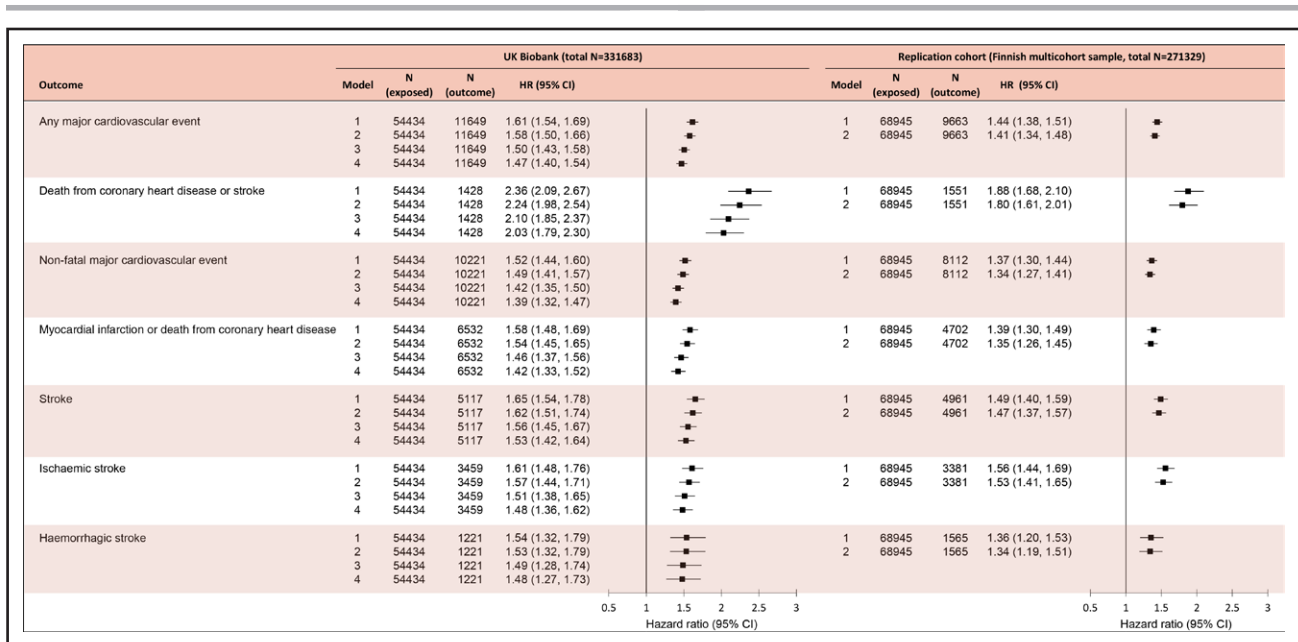
major cardiovascular events were recorded (incidence, 3.0 per 1000 person-years). Of these, 6532 were myocardial infarctions or coronary heart disease deaths, and 5117 were strokes.

In the replication cohort, one-quarter (n=68 945) of the 271 329 participants were hospitalized for an infection before a first major cardiovascular event. Of those participants, 36 253 had their first infection on or before baseline, and 32 692 had their first infection during follow-up (incidence, 7.7 per 1000 person-years). The most common infections were unspecified acute appendicitis (n=5969), unspecified pneumonia (n=5382), and unspecified gastroenteritis (n=5240). Additionally, 193 943 participants (71%) were hospitalized for non-infectious causes. During 5 219 865 person-years at risk after baseline, 9663 major cardiovascular events were recorded (incidence, 1.9 per 1000 person-years). Of these, 4702 were myocardial infarctions or coronary heart disease deaths, and 4961 were strokes.

Figure 1 shows that a higher risk of any major cardiovascular event and specific cardiovascular end points (cardiovascular death, nonfatal major cardiovascular event, myocardial infarction or coronary heart disease death, stroke, ischemic stroke, or hemorrhagic stroke) was related to previous severe infection across the full follow-up period in both the UK Biobank and the replication cohort. In multivariable-adjusted analyses, there was evidence of partial attenuation, such that for all cardio-

vascular outcomes, the greater the number of traditional cardiovascular risk factors controlled for, the greater the level of attenuation. However, all infection–outcome associations were retained at conventional levels of statistical significance. The association between infections and major cardiovascular events also remained in analyses controlling for the competing risk of noncardiovascular deaths (Figure S4).

The risk of a major cardiovascular event was most strongly related to infection, regardless of the type, during the first month of exposure (Figure 2). The strongest associations were seen for pneumonia (HR, 11.9 [UK Biobank] and 10.8 [replication cohort]) and viral infections (12.8 and 9.2, respectively). In the UK Biobank, the incidence of major cardiovascular events within the first month from infection was 2.59 (95% CI, 2.10–3.19) per 1000 person-months, which corresponds to 31.5 (95% CI, 25.6–38.8) per 1000 person-years. In the replication cohort, the incidence was 1.67 (95% CI, 1.23–2.13) per 1000 person-months (20.3 [95% CI, 15.0–25.9] per 1000 person-years). Consistent patterns of association were also seen in analyses stratified by calendar period and in subgroups of high versus low socioeconomic status, diabetes versus no diabetes, hypertension versus no hypertension, smoking versus no smoking, and female versus male sex (Figure S5). Most of the relative risk estimates were higher for women than for men. The pattern of association remained similar in sensitivity



**Figure 1. Serial-adjusted risk of cardiovascular disease outcomes associated with severe (hospital-treated) infectious disease in the UK Biobank and replication cohorts.**

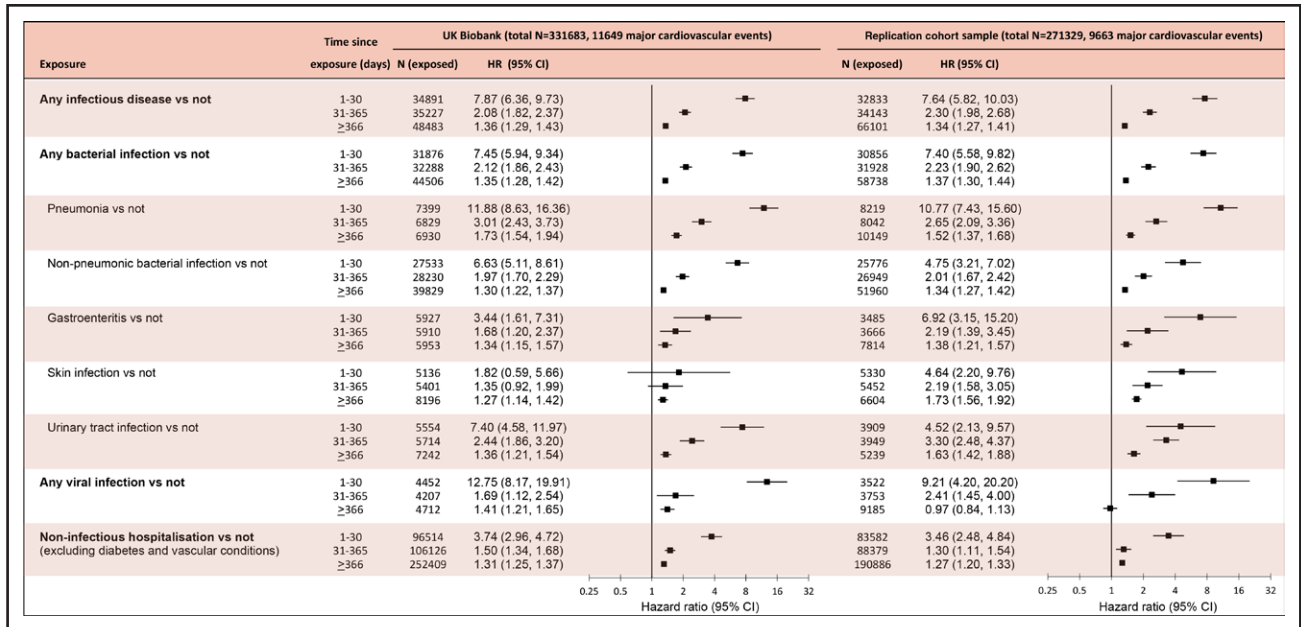
Model 1 is adjusted for age, sex, and socioeconomic status. Model 2 is adjusted for age, sex, socioeconomic status, hypertension, and diabetes. Model 3 is adjusted for age, sex, socioeconomic status, hypertension, diabetes, smoking, alcohol consumption, low-density lipoprotein cholesterol, body mass index, and physical activity. Model 4 is adjusted for age, sex, socioeconomic status, hypertension, diabetes, smoking, alcohol consumption, low-density lipoprotein cholesterol, body mass index, physical activity, chronic liver disease, chronic kidney disease, chronic obstructive pulmonary disease, and asthma. HR indicates hazard ratio.

analyses restricted to incident infections, with follow-up restricted to the pre-COVID-19 era, hypertension, diabetes, and comorbidities treated as time-updated covariates, and after excluding participants with malignant tumours. This was also the case in analyses restricted to infections occurring at  $\geq 50$  years of age and with an alternative outcome definition that included arterial revascularization and thrombolysis in addition to hospitalizations and deaths from major cardiovascular events (Figures S6–S11). In further sensitivity analysis, the hazard of major cardiovascular event within the first month after hospitalization was 2.41-fold (95% CI, 1.48–3.93) in those hospitalized for infection compared with those hospitalized for other causes (Figure S12).

Most infections were also associated with an elevated rate of major cardiovascular events when  $>1$  year had passed since the infection, although the HRs were of lower magnitude (ranging from 1.3 [95% CI, 1.1–1.4] to 1.7 [95% CI, 1.6–1.9]; Figure 2). These relationships could be seen  $>10$  years after the infection (Figure S13). The only exception was viral infections in the replication cohort, which were no longer associated with increased cardiovascular risk  $>1$  year after infection. Hospitalization for noninfectious causes was also associated with a similar pattern of risk, but the short-term risk was lower than what was apparent for most infections (HR within the first month, 3.7 in the UK Biobank and 3.5 in the replication cohort). The pattern of high cardiovascular risk immediately after

infection and lower risk thereafter was also observed when infections were classified by severity and by site of infection as opposed to bacterial or viral infections (Figure 3). The greatest short-term risk was observed for sepsis (HR, 13.2 [within first month after the infection in the UK Biobank]; HR, 7.5 [replication cohort]) and lower respiratory tract infections (HR, 11.4 [within the first month after the infection in the UK Biobank]; 10.3 [replication cohort]). In the long term, sepsis was associated with higher cardiovascular risk than were nonseptic infections. Although the relative risk for cardiovascular events was similar regardless of the length of the initial hospitalization for infection (Figure S14), those with recurrent infections had a greater long-term risk than did those with only one infection (Figure 4). Infections were associated with a similar increased relative risk of cardiovascular disease in those with high, intermediate, borderline, and low estimated atherosclerotic cardiovascular disease risk (Figure S15), leading to the greatest increase in the number of major cardiovascular events after infection in the high-risk group and the lowest in the low-risk group (Table 2).

The weighted PAF of severe infections on major cardiovascular events was 4.4% in the UK Biobank and 6.1% in the replication cohort (Table 3). Given the 2.4 million cardiovascular deaths in high-income countries in 2019 as estimated by the GBD, this would translate to 110 000 to 150 000 deaths attributable to infections. For comparison, the weighted PAFs for smoking, hypertension,



**Figure 2. Risk of major cardiovascular event associated with any severe (hospital-treated), bacterial, and viral infections by time since infection in the UK Biobank and replication cohorts.**

In the UK Biobank, hazard ratios (HRs) were adjusted for age, sex, socioeconomic status, smoking, alcohol consumption, hypertension, diabetes, low-density lipoprotein cholesterol, body mass index, physical activity, chronic liver disease, chronic kidney disease, chronic obstructive pulmonary disease, and asthma. The analysis of noninfection hospitalizations was not adjusted for chronic liver disease, chronic kidney disease, chronic obstructive lung disease, and asthma because those were included in the definition of the exposure. In the replication cohort, HRs were adjusted for age, sex, socioeconomic status, hypertension, and diabetes.

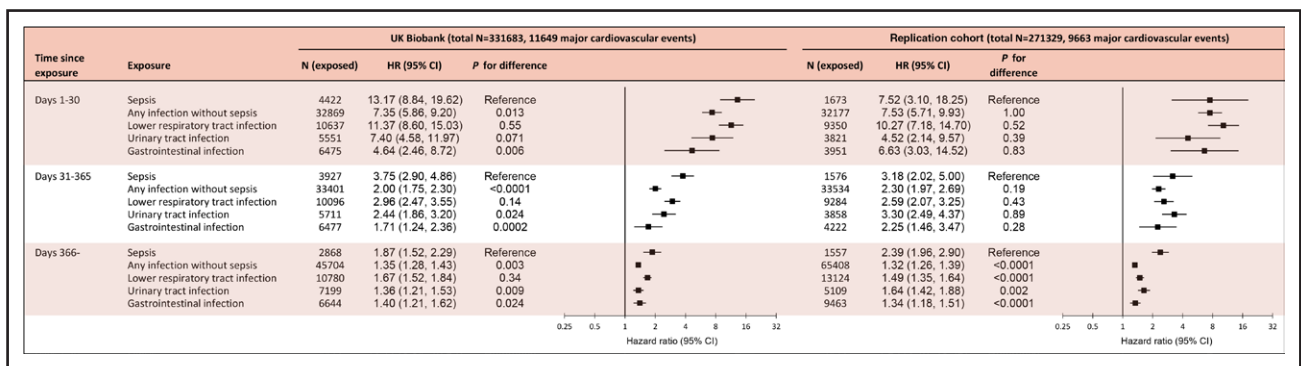
diabetes, and high LDL cholesterol ranged from 3.3% to 23.1% in the UK Biobank and from 2.3% to 19.7% in the replication cohort, depending on the risk factor.

**DISCUSSION**

In prospective cohorts from the United Kingdom and Finland, infectious diseases severe enough to require hospital treatment were associated with a large increase in the risk of major cardiovascular events during the first month after hospitalization. This risk diminished in time, but remained slightly increased in the long term

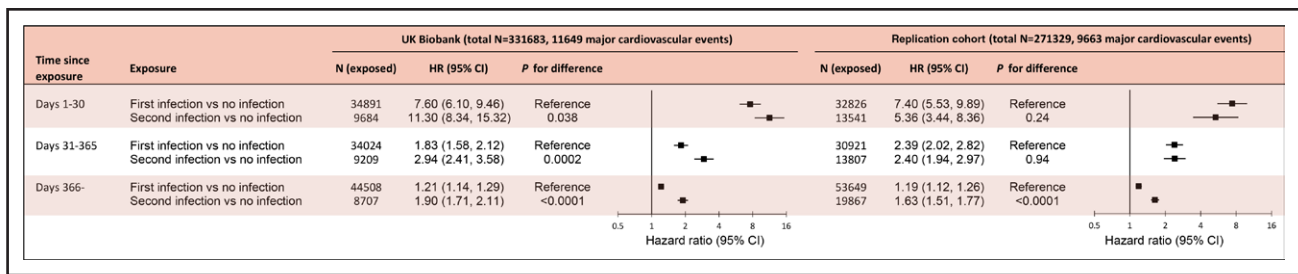
and did not seem to be specific to any particular type of infection. We estimated that 4.4% to 6.1% of cardiovascular events might be attributable to severe infections. The corresponding PAF was lower for diabetes (2.3–3.3%), but higher for hypertension (4.8–23.1%), dyslipidemia (12.3%), and smoking (9.7–19.7%) in our data sets.

Earlier evidence about specific infections supports our findings. Ecological studies show parallel seasonal trends in influenza and cardiovascular deaths,<sup>11,32,33</sup> and individual-level studies have reported strong short-term associations of respiratory tract infections (eg, influenza,



**Figure 3. Risk of major cardiovascular event associated with specific infections in the UK Biobank and replication cohorts.**

In the UK Biobank, hazard ratios (HRs) were adjusted for age, sex, socioeconomic status, smoking, alcohol consumption, hypertension, diabetes, low-density lipoprotein cholesterol, body mass index, physical activity, chronic liver disease, chronic kidney disease, chronic obstructive pulmonary disease, and asthma. In the replication cohort, HRs were adjusted for age, sex, socioeconomic status, hypertension, and diabetes.



**Figure 4. Risk of major cardiovascular event associated with the number of severe (hospital-treated) infections in the UK Biobank and replication cohorts.**

In the UK Biobank, hazard ratios (HRs) were adjusted for age, sex, socioeconomic status, smoking, alcohol consumption, hypertension, diabetes, low-density lipoprotein cholesterol, body mass index, physical activity, chronic liver disease, chronic kidney disease, chronic obstructive pulmonary disease, and asthma. In the replication cohort, HRs were adjusted for age, sex, socioeconomic status, hypertension, and diabetes.

COVID-19, and pneumonia), urinary tract infections, and bacteremia with myocardial infarction or major cardiovascular events. The relative risk estimates have ranged from 2.4 to 21.7 for respiratory tract infections, from 2.2 to 35.2 for bacteremia, and from 1.7 to 2.7 for urinary tract infections.<sup>2,4,6,7,34–36</sup> Our analyses on 931 diagnoses of infectious diseases with follow-up divided into 3 periods (ie,  $\leq 1$  month,  $>1$  month and  $\leq 1$  year, and  $>1$  year) substantially supplement this evidence base. We found that the increased short-term (1 month) risk for major cardiovascular events was evident for a wide range of hospital-treated infections, including bacterial and viral infections in general, as well as infections of specific sites (eg, respiratory and urinary tracts, and intestines). Although there was variation in the magnitude of the relative risks associated with different types of infection, the overall pattern of findings suggests that the increased

short-term cardiovascular risk may be a feature that is common to severe infections in general.

In addition to short-term associations, we found long-term associations of sepsis, pneumonia, and other bacterial infections with cardiovascular events. The risk of a major cardiovascular event remained elevated for more than a decade after infection. We also found a dose-response association between severity (septic versus nonseptic) and recurrence (single versus multiple hospitalizations) of infections and the long-term risk of cardiovascular events. These findings accord with previous studies, in which multivariable-adjusted long-term relative hazards for cardiovascular events ranged between 1.63 and 1.89 for pneumonia,<sup>2</sup> and between 1.27 and 2.30 for sepsis.<sup>3,37</sup> However, increased long-term risk after infection is not a universal observation: in one investigation, the increased cardiovascular disease risk was found only

**Table 2. Absolute Risk of Major Cardiovascular Events Associated With Severe (Hospital-Treated) Infection by Estimated Risk of ASCVD at Baseline and Time Since Infection in the UK Biobank**

Ten-year risk of ASCVD at baseline	Time since severe infection	No. severe infection	No. events among those with severe infection	Incidence (95% CI) of major cardiovascular events per 1000 person-years
Low*	1–30 days	11 024	11	12.3 (6.8–22.2)
	31–365 days	11 463	29	2.9 (2.0–4.1)
	366+ days	17 322	209	2.1 (1.7–2.5)
Borderline†	1–30 days	4099	11	33.4 (18.5–60.2)
	31–365 days	4161	22	6.9 (4.6–10.2)
	366+ days	5795	184	5.1 (4.1–6.3)
Intermediate‡	1–30 days	11 474	27	29.5 (20.2–43.0)
	31–365 days	11 480	93	10.2 (8.3–12.4)
	366+ days	14 955	683	7.7 (6.9–8.6)
High§	1–30 days	4983	32	81.7 (57.8–115.5)
	31–365 days	4797	60	15.6 (12.2–19.9)
	366+ days	5763	480	14.9 (13.1–16.9)

Ten-year risk of ASCVD at baseline was estimated using the American College of Cardiology/American Heart Association Pooled Cohort Equations. ASCVD indicates atherosclerotic cardiovascular disease.

\*Low-risk,  $<5\%$ .

†Borderline-risk,  $5\%$  to  $<7.5\%$ .

‡Intermediate-risk,  $7.5\%$  to  $<20\%$ .

§High-risk,  $\geq 20\%$ .

**Table 3. Population-Attributable Fractions of Severe Infections and Standard Cardiovascular Risk Factors on Major Cardiovascular Events**

Risk Factor	UK Biobank	Replication cohort (Finnish multicohort sample)	High-income countries (PURE study)*	High-income countries (GBD 2019)†
Severe infections	4.4	6.1	–	–
Smoking	9.7	19.7‡	15.7	9.5
Hypertension	23.1	4.8	14.6	31.3
Diabetes	3.3	2.3	7.8	15.7
High LDL cholesterol	12.3	–	20.7	18.7
Joint PAF	52.9	33.0	58.8	75.3

Data expressed in percentages (%). Reported PAFs are weighted to reflect the contribution of each risk factor to the total PAF. Details of the PAF computations and definitions of risk factors in each study are reported in [Tables S4 and S5](#).

– indicates data not available; GBD 2019, Global Burden of Disease Study 2019; LDL, low-density lipoprotein; PAF, population-attributable fraction; and PURE study, Prospective Urban Rural Epidemiology study.

\*Data from Yusuf S et al<sup>24</sup> in which non–high-density lipoprotein cholesterol was used instead of LDL cholesterol.

†Data are from GBD 2019 Risk Factors Collaborators<sup>27</sup> and the GBD Results Tool (<http://ghdx.healthdata.org/gbd-results-tool>). Cardiovascular deaths (the combination of coronary heart disease and stroke deaths) were used instead of major cardiovascular events, for which data were not available.

‡Smoking data are from a subcohort (n=121 899 [of 273 316]) with such data available.

during the first 30 days after bacteremia,<sup>4</sup> and in another study, the association was evident only during the first 7 days after influenza.<sup>1</sup>

Part of the observed excess risk in individuals with a history of severe infection could be attributable to misclassification of infection-related deaths as cardiovascular deaths among participants with underlying cardiovascular disease. However, this is an unlikely explanation for our findings, as the excess risk was also observed for non-fatal cardiovascular disease events. Hospitalization from noninfectious causes showed a weaker short-term association with cardiovascular disease events than did hospitalizations from infection, suggesting that the short-term association of severe infections with cardiovascular disease is not attributable to the nonspecific effects of simply being hospitalized. This inference is strengthened by a sensitivity analysis in which we used participants hospitalized from noninfectious causes as the comparison group instead of all those not hospitalized for infections. The association between infections and cardiovascular events remained strong; there was >2-fold increased risk of cardiovascular disease during the first month after infection.

A further potential source of bias is the higher prevalence of conventional cardiovascular disease risk factors, such as smoking and obesity, among those with severe infections. Confounding by these risk factors is likely to have different roles in the short- and longer-term risk of cardiovascular disease. The observed time-dependent association characterized by the abrupt increase of cardiovascular disease risk immediately after an infection, and its rapid decline thereafter, is not consistent with the temporal pattern of risk associated with conventional cardiovascular risk factors.<sup>6,38</sup> This suggests that infections may act as triggers of acute cardiovascular events, particularly in the presence of underlying atherosclerosis. By contrast, the somewhat increased long-term postinfection risk could well be explained by residual

confounding even after adjustment for standard cardiovascular risk factors, as unmeasured differences in these risk factors or other health problems could increase the risk of both being hospitalized for an infection and experiencing a cardiovascular event.

Several plausible mechanisms might explain why infections could trigger acute cardiovascular events. Acute infection increases metabolic needs and heart rate. This increases the oxygen need of myocardial cells and decreases oxygen supply to the heart by shortening the filling time of coronary arteries during diastole, a combination of changes that predisposes to demand ischemia, which is also known as type 2 myocardial infarction.<sup>13</sup> Increased levels of catecholamines and inflammatory cytokines may contribute to arrhythmias, and infections might also cause direct myocardial damage.<sup>13</sup> Furthermore, infections may increase inflammation in atheromatous plaques, making them less stable, and move the body into a prothrombotic state, increasing the risk of blood clots that can block an artery.<sup>12,13,39</sup> There is also some evidence suggesting that inflammatory changes could persist after resolution of the acute phase of a severe infection.<sup>14,40</sup>

We evaluated societal impacts using the population-attributable fraction, a statistic that integrates the prevalence of the risk factor in the population and the strength of its association with the outcome being considered. The core assumption in this calculation is that the risk factor has a causal impact on the outcome. If the long-term associations observed in this study are indeed causal, the considerable estimated burden of infection-related cardiovascular events suggests that more effective prevention of infectious diseases will reduce the population-level occurrence of cardiovascular disease. However, in addition to the uncertainty of the causality assumption, further uncertainty arises from the considerable variation in the PAF estimates between cohort studies featured in our analyses, possibly reflecting differences in study

populations and the measures of cardiovascular risk factors. For a more accurate determination of the burden of cardiovascular disease attributable to infections and traditional risk factors, future studies should aim to rely on representative population samples and uniform assessment of both infections and cardiovascular risk factors.

## Strengths and Limitations

The strengths of this study include large sample size, systematic assessment of hospitalizations for a wide range of infectious diseases at the level of specific diagnoses, and disease ascertainment on the basis of nationwide register data with high coverage, allowing a virtually complete follow-up and uniform assessment of participants, which was not dependent on a person's active participation in study examinations during follow-up. The results were replicated in a different setting with considerably younger participants. This strengthens the robustness and generalizability of our findings.

There are also several limitations. Our approach, which focused on severe, hospital-treated infections, may have overestimated the relative risk of major cardiovascular events associated with infections but underestimated the overall contribution of infections on the burden of cardiovascular disease, as we could only record infections that were severe enough to warrant hospitalization, thus missing the potential impact of milder infections, which constitute the majority of all infections.<sup>10</sup> We categorized infections to reflect major clinical entities, but we recognize that other categorizations could also have been chosen. We assumed that pneumonia and urinary tract infection cases without a specified cause would be bacterial, which may have led to misclassification of some viral pneumonia cases. Standard PAF computations are intended for chronic risk factors, whereas most infections resolve quickly after an initial acute phase. However, we believe that our approach of using the association of infections with cardiovascular events from the entire follow-up period in our PAF computations is a reasonable approximation of the overall association between infections and cardiovascular disease.

Further limitations include possible residual confounding from inaccurate or lacking measurement of relevant confounders, which may have contributed to overestimation of associations. We could not analyze treatments for infections or admission to intensive care. Response rate was low in the UK Biobank, but observed risk factor–disease associations have been in agreement with those from more representative samples.<sup>41</sup> All data were from high-income countries. Future studies should assess the generalizability of our findings in low- and middle-income countries.

## Clinical Implications

Our findings show that the absolute cardiovascular risk associated with severe infections is highest among

people with preexisting elevated risk for cardiovascular disease. In clinical settings, use of conventional risk estimators, such as the American College of Cardiology/American Heart Association pooled cohort equations for 10-year atherosclerotic cardiovascular disease risk, helps to identify these people.<sup>42</sup> Although particular attention may be required for this group because of their increased risk of infection-related cardiovascular events, treatment decisions must account for the risk of major intracranial and gastrointestinal bleeding, which may also be increased in the acute phase of an infection.<sup>43–45</sup> Avoidance of potential triggers of cardiac and cerebrovascular events during the acute phase, such as excessive use of alcohol, overeating, lack of sleep, work stress, and long working hours, may be beneficial and is without harm.<sup>46,47</sup>

## CONCLUSIONS

Our findings indicate a substantially increased short-term risk of cardiovascular and cerebrovascular events immediately after severe infections. We also observed a modest long-term excess risk of these events, but residual confounding cannot be excluded.

## ARTICLE INFORMATION

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### Affiliations

Departments of Public Health (P.N.S., J.V.L., S.T.N., J.P., M.K.) and Bacteriology and Immunology and Translational Immunology Research Program, University of Helsinki, Finland (N.H., S.M.). Finnish Institute of Occupational Health, Helsinki (P.N.S., A.V., A.K., S.T.N., J.P., M.K.). UCL Brain Sciences (J.V.L., G.D.B., M.K.) and Institute of Epidemiology and Health Care (A.C.H.), University College London, UK. Department of Public Health, University of Turku, Finland (J.V., S.S., J.P.). Centre for Population Health Research, University of Turku and Turku University Hospital, Finland (J.V.). Turku University Hospital, Finland (S.S.). School of Health and Education, University of Skövde, Sweden (S.S.). HUSLAB, Helsinki University Hospital, Finland (S.M.). Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, United Kingdom (C.W.-G.).

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## Supplemental Material

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