ESC European Society of Cardiology

European Heart Journal Open (2025) **5**, oeaf009
https://doi.org/10.1093/ehjopen/oeaf009

ORIGINAL ARTICLE
Cardiovascular genetics

Low LDL cholesterol and risk of bacterial and viral infections: observational and Mendelian randomization studies

Marianne Benn [1,2,3,*], Frida Emanuelsson [1], Anne Tybjærg-Hansen[1,2,3,4], and Børge G. Nordestgaard [2,3,4,5]

[1]Department of Clinical Biochemistry, Copenhagen University Hospital—Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark; [2]The Copenhagen General Population Study, Copenhagen University Hospital—Herlev and Gentofte, Borgmester Ib Juuls vej 1, DK-2730 Herlev, Denmark; [3]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 3, DK-2200 Copenhagen, Denmark; [4]The Copenhagen City Heart Study, Copenhagen University Hospital—Bispebjerg and Frederiksberg, Bispebjerg Bakke 23, DK-2400 Copenhagen, Denmark; and [5]Department of Clinical Biochemistry, Copenhagen University Hospital—Herlev and Gentofte, Borgmester Ib Juuls vej 1, DK-2730 Herlev, Denmark

Received 11 December 2024; revised 13 January 2025; accepted 31 January 2025; online publish-ahead-of-print 3 February 2025

Handling Editor: Susanna C. Larsson

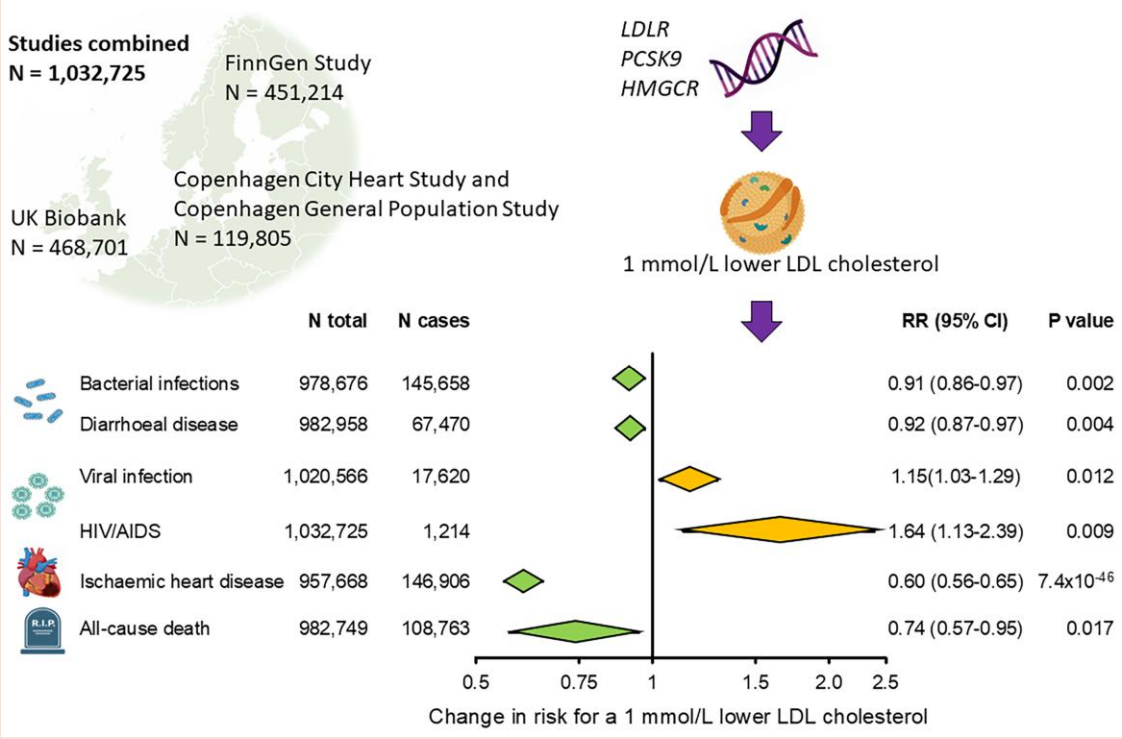
Aims Low levels of LDL cholesterol may be associated with risk of infectious disease. We tested the hypothesis that low LDL cholesterol due to genetic variation in the *LDLR*, *PCSK9*, and *HMGCR* genes and a polygenic LDL cholesterol score is associated with risk of infectious diseases in the general population.

Methods and results Using observational and Mendelian randomization designs, we examined associations of low plasma LDL cholesterol with risk of bacterial and viral infections in 119 805 individuals from the Copenhagen General Population Study/Copenhagen City Heart Study, 468 701 from the UK Biobank, and up to 376 773 from the FinnGen Research Project. Observationally, low LDL cholesterol concentrations were associated with risk of hospitalization for both bacterial and viral infections. In genetic analyses, a 1 mmol/L lower LDL cholesterol was associated with lower plasma PCSK9 {−0.55 nmol/L [95% confidence interval (CI): −1.06 to −0.05]; $P = 0.03$}, leucocyte count [-0.42×10^9/L (−0.61 to −0.24); $P < 0.001$], and high-sensitivity C-reactive protein [−0.44 mg/L (−0.79 to −0.09); $P = 0.014$]. Using an *LDLR*, *HMGCR*, and *PCSK9* score, a 1 mmol/L lower LDL cholesterol was associated with risk ratios of 0.91 (95% CI: 0.86–0.97; $P = 0.002$) for unspecified bacterial infection, of 0.92 (0.87–0.97; $P = 0.004$) for diarrhoeal disease, and of 1.15 (1.03–1.29; $P = 0.012$) for unspecified viral infections and 1.64 (1.13–2.39; $P = 0.009$) for HIV/AIDS. Using a polygenic LDL cholesterol score largely showed similar results and in addition a lower risk of 0.85 (0.76–0.96; $P = 0.006$) for bacterial pneumonia and 0.91 (0.82–0.99; $P = 0.035$) for sepsis.

Conclusion Genetically low LDL cholesterol concentrations were associated with lower concentration of markers of inflammation; lower risk of hospitalization for unspecified bacterial infections, infectious diarrhoeal diseases, bacterial pneumonia, and sepsis; and higher risk of viral infections and HIV/AIDS.

* Corresponding author. Tel: +45 3545 3040, Email: Marianne.benn@regionh.dk

Graphical abstract



Keywords LDL cholesterol • Lipid lowering • Statin • Bacterial infection • Infectious diarrhoeal disease • Viral infection

Introduction

During bacterial infections, lipopolysaccharides are shredded from bacterial cell membranes, activating the innate immune response and causing inflammation. Lipopolysaccharides are integrated into lipoprotein particles and removed via the LDL and very LDL (VLDL) receptor pathways. Studies have suggested that increasing the number of LDL receptors with lipid-lowering drugs during septic shock reduces short-term risk of death.[1–3] On the other hand, some viruses can bind directly to these receptors and be taken up into the cells and facilitate virus replication.[4,5]

Theoretically, this means that low LDL cholesterol, i.e. by increasing the number of LDL receptors by statins or the number of LDL and VLDL receptors by proprotein convertase subtilisin kexin type 9 (PCSK9) inhibition, may be beneficial during bacterial infections clearing lipopolysaccharides and harmful during viral infections facilitating virus uptake and replication.[1,2,4–6]

Genetic variation in the *LDLR*, *PCSK9*, and *HMGCR* genes encoding, respectively, the LDL receptor, PCSK9, and the 3-hydroxy-3-methylglutaryl-CoA reductase mimic the effect of lipid lowering by statins and PCSK9 inhibitors.[7] We hypothesized that low LDL cholesterol concentration due to genetic variation in these specific genes, potentially improving clearance of inflammatory lipopolysaccharides and potentially increasing uptake of virus, is associated with low risk of bacterial infections and high risk of viral infections. We tested this hypothesis in observational and Mendelian randomization designs with hospitalization for specific infectious diseases as outcomes/endpoints. The Mendelian randomization design utilizes the random assortment of alleles at conception, and used in a general population setting, the design is largely unaffected by survivor bias, reverse causation, and confounding.[8,9] To examine whether potential changes in risk were due to specific involvement of the LDL receptor and PCSK9 protein or simply due to lower LDL cholesterol in general, we used both a target *LDLR*, *PCSK9*, and *HMGCR* genetic score using variants in the *LDLR*, *PCSK9*, and *HMGCR* genes and a polygenic LDL cholesterol score, not including these genes. This has not been examined previously.

The hypotheses were tested in three steps: (i) the observational association of LDL cholesterol concentration with risk of bacterial and viral infections in two cohorts from the Danish general population, the Copenhagen General Population Study (CGPS) and the Copenhagen City Heart Study (CCHS), and the UK Biobank cohort; (ii) the association of a genetic score of LDL lowering alleles (*LDLR*, *PCSK9*, and *HMGCR* genetic variants) and a polygenic LDL cholesterol score excluding these variants, with LDL cholesterol, PCSK9, leucocyte count, and C-reactive protein; and (iii) the causal genetic effect of a 1 mmol/L lower plasma LDL cholesterol on risk of bacterial and viral infections in the two Copenhagen cohorts and the UK Biobank cohort[10] using individual data information, while using summary data from the Global Lipids Genetics Consortium (GLGC)[11] and FinnGen Research Project in a two-sample design and, finally, combined results from all cohorts in meta-analyses.

Methods

Study populations

We included individuals from two similar prospective studies of the Danish general population, the CGPS and the CCHS.[12] Combining the two studies

for observational examinations yielded a total of 119 805 individuals with information on both LDL cholesterol concentration and genotype data. All individuals were white and of Danish descent, none was included in more than one study, and no individuals were lost to follow-up due to the complete Danish health registries. Information on the UK Biobank,[10] GLGC,[13] and FinnGen Research Project[14] is summarized in Supplementary Appendix 1.

Ethical reporting

The study was conducted in accordance with the Declaration of Helsinki, and CGPS and CCHS were approved by the Danish ethical committees (KF-100.2039/91, KF-01-144/01, and H-KF-01-144/01), the UK Biobank study by the North West Haydock Research Ethics Committee (16/NW/0274), and the FinnGen by the Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District. Written informed consent was obtained from all participants.

Study endpoints/outcomes

In the Copenhagen studies, we used the Danish National Patient Register[15] which covers all Danish hospitals with information on hospitalizations, outpatient, and/or emergency room visits with a primary discharge diagnosis of an infectious disease. In the Copenhagen studies, infectious disease diagnoses were classified according to the World Health Organization's International Statistical Classification of Diseases 8th and 10th Revision (ICD-8 and ICD-10) and in the UK Biobank and the FinnGen Research Project using ICD-8, ICD9, and ICD-10. In all studies, codes were harmonized across the three revisions and collapsed into the following categories of bacterial infections: any bacterial infection including unspecified bacterial infections, infectious diarrhoeal disease, bacterial pneumonia, sepsis, urinary tract infections/cystitis, endocarditis, skin infections, and bacterial meningitis and viral diseases: any viral infection including unspecified viral infection, human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS), hepatitis, viral meningitis, and viral pneumonia (see Supplementary material online, *Table S1*). Categories of infectious diseases in the CCHS have been validated and found to correspond well to discharge diagnoses and positive culture findings.[16] In the Copenhagen studies and the UK Biobank, follow-up time began at the first inclusion into a study and ended with censoring at date of death, occurrence of an event, emigration, or end of follow-up on 13 December 2018 in the Copenhagen studies and 21 March 2023 in the UK Biobank, whichever came first. In the FinnGen Research Project, data from Release 11 was used (released on 27 June 2024).

Covariates

In the Copenhagen studies, plasma LDL cholesterol was calculated using the Friedewald equation if plasma triglycerides were ≤4.0 mmol/L and measured by a direct enzymatic method at higher triglyceride concentrations. Plasma total cholesterol, HDL cholesterol, triglycerides, and high-sensitive C-reactive protein and blood leucocytes were measured using standard hospital assays. Plasma PCSK9 was measured by BG Medicine (Waltham, MA, USA) with a sandwich ELISA assay using antibodies supplied by Merck (Whitehouse Station, NJ, USA).

Participants reported on smoking (current smokers and non-smokers); work and leisure time physical activity ('low' for 0–2 h moderate activity per week and 'intermediate and high' for more than 2 h moderate or vigorous activity per week during either work or leisure time); alcohol consumption in units per week (1 unit ∼12 g alcohol); education (<8 and ≥8 years of completed education); use of cholesterol-lowering medication with more than 97% using statins; and for women, menopausal status. Body mass index was weight/height squared. Hypertension was defined as systolic blood pressure ≥ 140 mmHg (≥135 mmHg for individuals with diabetes), diastolic blood pressure ≥ 90 mmHg (≥85 mmHg for individuals with diabetes), or use of antihypertensive medication prescribed specifically for hypertension. Diabetes mellitus was self-reported disease, a non-fasting plasma glucose > 11.0 mmol/L, medication prescribed for diabetes and/or hospitalization due to diabetes (ICD-8 249–250; ICD-10 E10–11, E13–14). Non-skin cancer was defined as any cancer—basal cell carcinoma not included. Ischaemic heart disease was defined as hospitalization due to ischaemic heart disease (ICD-8 410–414; ICD-10 I20-I25).

Genetic instruments: targeted approach and polygenic LDL cholesterol score

In the Copenhagen studies, an ABI PRISM 7900HT (Applied Biosystems, USA) and TaqMan-based assays were used to genotype for LDL cholesterol associated variants in the *LDLR*, *PCSK9*, and *HMGCR* genes. Variants for the polygenic LDL cholesterol score were genotyped using the customized Metabochip[17] and the Infinium HumanExome BeadChip (Illumina, San Diego, CA, USA). Variants were selected based on their association with plasma LDL cholesterol in genome-wide association studies, either as variants in the *LDLR*, *HMGCR*, or *PCSK9* genes for the target approach or genome-wide, excluding the three genes above (±100 000 base pairs up- and downstream from the three genes) for the polygenic risk score. For *LDLR*, *HMGCR*, or *PCSK9* variants, their functions are well-known and pleiotropic effects have not been observed.[12] Also, none of the variants should not be in linkage disequilibrium (LD) using a threshold of $R^2 < 0.3$. If possible, the same variants were selected in the UK Biobank and GLGC/FinnGen Research Project, or else proxies (LD > 0.90) or other LDL cholesterol associated variants were selected (see Supplementary material online, *Tables S2* and *S3*). In the Copenhagen studies and the UK Biobank, weighted allele scores were constructed by summation of LDL cholesterol-decreasing alleles, weighted by allele frequency and effect size on plasma LDL cholesterol, as done previously (see Supplementary material online, *Figure S1*).[18] The *LDLR*, *HMGCR*, or *PCSK9* variants explained 0.5% of the variation in plasma LDL cholesterol in the Copenhagen studies and 0.8% in the UK Biobank; and the polygenic LDL cholesterol score explained 0.6% of the variation in plasma LDL cholesterol in the Copenhagen studies and 1.8% in the UK Biobank.

Statistical analysis

We used Stata SE 17.0 (StataCorp). Deviation from the Hardy–Weinberg expectations was tested using Pearson's χ^2 test. To test whether plasma LDL cholesterol was observationally associated with risk of bacterial and viral diseases, we used Cox regression and restricted cubic splines with three knots, selected using the Akaike's information criterion.[19] Adjustments were done for potential confounders, including age (as underlying time scale), sex, year of birth, body mass index, smoking, physical activity, alcohol consumption, education, hypertension, type 2 diabetes mellitus, and non-skin cancer. Adjustment for year of birth was included to accommodate changes in diagnostic criteria and treatment over calendar time.

To test whether LDL cholesterol alleles were associated with plasma LDL cholesterol, PCSK9, leucocyte count, and C-reactive protein, analyses of variance was used. Tests for trend across ordered categories of concentrations and the weighted allele score were by the non-parametric Cuzick's extension of a Wilcoxon rank sum test. Logistic regression was used to assess whether observational lower LDL cholesterol or the allele score was associated with the potential confounders of age, sex, body mass index, smoking, physical activity, alcohol consumption, education, hypertension, type 2 diabetes, and non-skin cancer.

The effect of genetically lower plasma LDL cholesterol concentration on risk of infectious diseases was estimated using instrumental variable analysis by two-stage least-squares regression using the user-written *ivreg2* and *ivpois* commands.[20] The statistical strength of the genetic instrument was confirmed by *F* statistics for the weighted allele score of $F = 144.8$ and $F = 981.4$ in the Copenhagen studies and the UK Biobank, respectively, where $F > 10$ is considered acceptable.[21] Sargan's statistic for the weighted allele score indicated that the genetic variants were valid instruments, with no indication of heterogeneity/pleiotropy (all $P > 0.36$).[22]

Estimates of the causal effect of plasma LDL cholesterol on risk of infectious disease from summary-level data from the GLGC[23] and the FinnGen Research Project[14] were obtained by regression analyses using inverse-variance-weighted and Egger regression,[20] in the user-written *mregger* command in Stata.[20,24] Because Egger regression did not indicate pleiotropy of genetic variants (largest intercept = 0.01; $P = 0.33$), results were reported as inverse-variance-weighted estimates. The Bonferroni method was used to correct for multiple testing with an overall α=0.05 and a Bonferroni corrected α=0.05/(number of hypotheses tested, i.e. endpoints tested).[25]

A causal effect summary estimate for the Copenhagen studies, UK Biobank, and GLGC/FinnGen studies was obtained by meta-analysis using the *metan* command with a random effects model.

Table 1 Baseline characteristics of participants in the Copenhagen City Heart Study and the Copenhagen General Population Study (Copenhagen studies) and the UK Biobank

	Copenhagen studies	UK Biobank
Number of individuals	119 805	468 701
Age, years	56 (46–66)	58 (50–63)
Sex, women	62 749 (55%)	229 085 (45%)
Ethnicity		
White	119 805 (100%)	442 662 (94.4%)
Asian	0 (0%)	11 070 (2.4%)
Black	0 (0%)	7175 (1.5%)
Mixed	0 (0%)	1982 (0.4%)
Other	0 (0%)	5812 (1.2%)
LDL cholesterol, mmol/L	3.3 (2.7–4.0)	3.5 (2.9–4.1)
HDL cholesterol, mmol/L	1.56 (1.24–1.94)	1.39 (1.17–1.67)
Triglycerides, mmol/L	1.39 (0.96–2.05)	1.48 (1.04–2.15)
Body mass index, kg/m^2	25.4 (23.0–28.3)	26.7 (24.1–29.9)
Menopause in women (%)	38 112 (61%)	165 380 (72%)
Current smoking (%)	28 120 (25%)	52 962 (11%)
Physical activity		
Low	55 550 (48%)	162 450 (49%)
Moderate	49 819 (43%)	95 068 (29%)
High	9505 (8.3%)	73 684 (22%)
Alcohol, units/week	7 (2–14)	9 (5–15)
Hypertension (%)	26 916 (23%)	269 906 (54%)
Education, longer than 8 years	30 051 (27%)	—
Lipid-lowering treatment (%)	10 838 (9.5%)	86 878 (17%)
Diabetes mellitus (%)	4148 (3.6%)	26 496 (5.3%)
Ischaemic heart disease (%)	18 118 (16%)	56 494 (12%)
Bacterial infection, not specified	36 550 (32%)	88 422 (18%)
Viral infection, not specified	1516 (1.3%)	8834 (1.9%)

The Copenhagen studies were used for observational and Mendelian randomization analyses. The UK Biobank was used for Mendelian randomization analyses. Data are absolute numbers (%) for categorical variables and median (interquartile range) for continuous variables. Units of alcohol/week is for individuals currently drinking alcohol, and 1 unit corresponds to 12 g.

Results

Participant characteristics

In the Copenhagen studies, up to 119 805 individuals were included for observational and Mendelian randomization analyses, and in the UK Biobank, 468 701 individuals were included for observational and genetic Mendelian randomization analyses. The GLGC and FinnGen Research Project included 188 577 and up to 451 201 individuals for genetic Mendelian randomization analyses, respectively. Genotype distributions did not deviate from Hardy–Weinberg expectations in any of the studies (all $P > 0.05$). Baseline characteristics of the Copenhagen studies and UK Biobank participants by study are shown in *Table 1*. Such data were not available for the FinnGen Research Project. Individuals in the Copenhagen studies and the UK Biobank were of a similar age at study entry, with largely similar percentages of women and men. The Copenhagen studies included only white individuals and the UK Biobank 94% white, 2.4% Asian, 1.5% black, 0.4% mixed, and 1.2% other individuals. Individuals in the UK Biobank had slightly higher body mass index, and a larger fraction had hypertension and diabetes and received lipid-lowering treatment, compared to the Copenhagen studies. In the Copenhagen studies, there was a larger fraction of smokers, individuals with ischaemic heart disease, and individuals having had bacterial infections, compared to the UK Biobank.

LDL cholesterol and observational risk of bacterial and viral infections

Compared with the population median for plasma LDL cholesterol concentration of 3.3 mmol/L, a lower LDL cholesterol concentration was during a median of 9.7 years follow-up (range 0–42.8) associated with higher observational prospective risks of hospitalization for any bacterial or viral infection, while a high concentration did not associate with risk ($P < 0.001$) (*Figure 1*, upper panel). Similar results were found in the UK Biobank study (see Supplementary material online, *Figure S2*). An LDL cholesterol concentration below 2 mmol/L was associated with a hazard ratio for any bacterial infection of 1.32 [95% confidence interval (CI): 1.24–1.41; $P < 0.001$] and for any viral infection of 1.60 (1.17–2.19; $P < 0.001$), compared to individuals with an LDL cholesterol ≥ 3 mmol/L (*Figure 1*, lower panel).

Confounding factors in observational and genetic analyses

Observationally, high age, male sex, high body mass index, smoking, high physical activity, high alcohol consumption, education ≥ 8 years, hypertension, type 2 diabetes, non-skin cancer, and ischaemic heart disease were all associated with both plasma LDL cholesterol and bacterial and viral infections and may therefore have confounded the observational associations (see Supplementary material online, *Figure S3*). However, the genotypes were either not or only modestly associated with any of the potential confounders, suggesting that a pleiotropic effect through any of the above factors is limited.

Genetic score, plasma LDL cholesterol, PCSK9, hsCRP, and leukocyte count

A weighted allele score consisting of genetic variants in the *LDLR*, *PCSK9*, and *HMGCR* genes was associated with stepwise lower plasma LDL cholesterol ($P < 0.0001$) and PCSK9 concentrations ($P < 0.0004$) and blood leucocyte count ($P < 0.0001$) (*Figure 2*, upper panels). In instrumental variable analysis, a 1 mmol/L lower LDL cholesterol reduced plasma PCSK9 by 0.55 nmol/L (−1.06 to −0.05; $P = 0.033$), leucocyte count by 0.42×10^9/L (−0.61 to −0.24; $P < 0.001$), and hsCRP by 0.44 mg/L (−0.79 to −0.09; $P = 0.014$) (*Figure 2*, lower panel).

Genetic low LDL cholesterol and risk of bacterial infections

For the *LDLR*, *HMGCR*, and *PCSK9* genetic score, a 1 mmol/L lower LDL cholesterol was associated with age- and sex-adjusted causal risk ratios of 0.91 (95% CI: 0.86–0.97; $P = 0.002$) for unspecified bacterial infection and sex-adjusted causal risk ratios of 0.92 (0.87–0.97; $P = 0.004$) for diarrhoeal disease in studies combined (*Figure 3*). Individual study estimates are shown in Supplementary material online, *Figure S4*. Using a polygenic LDL cholesterol score, a 1 mmol/L lower LDL cholesterol was associated with age- and sex-adjusted causal risk ratios of 0.88 (0.81–0.95; $P = 0.001$) for unspecified bacterial infection, of 0.94 (0.89–1.00; $P = 0.053$) for diarrhoeal disease, of 0.85 (0.76–0.96; $P = 0.006$) for bacterial pneumonia, of 0.91 (0.82–0.99; $P = 0.035$) for

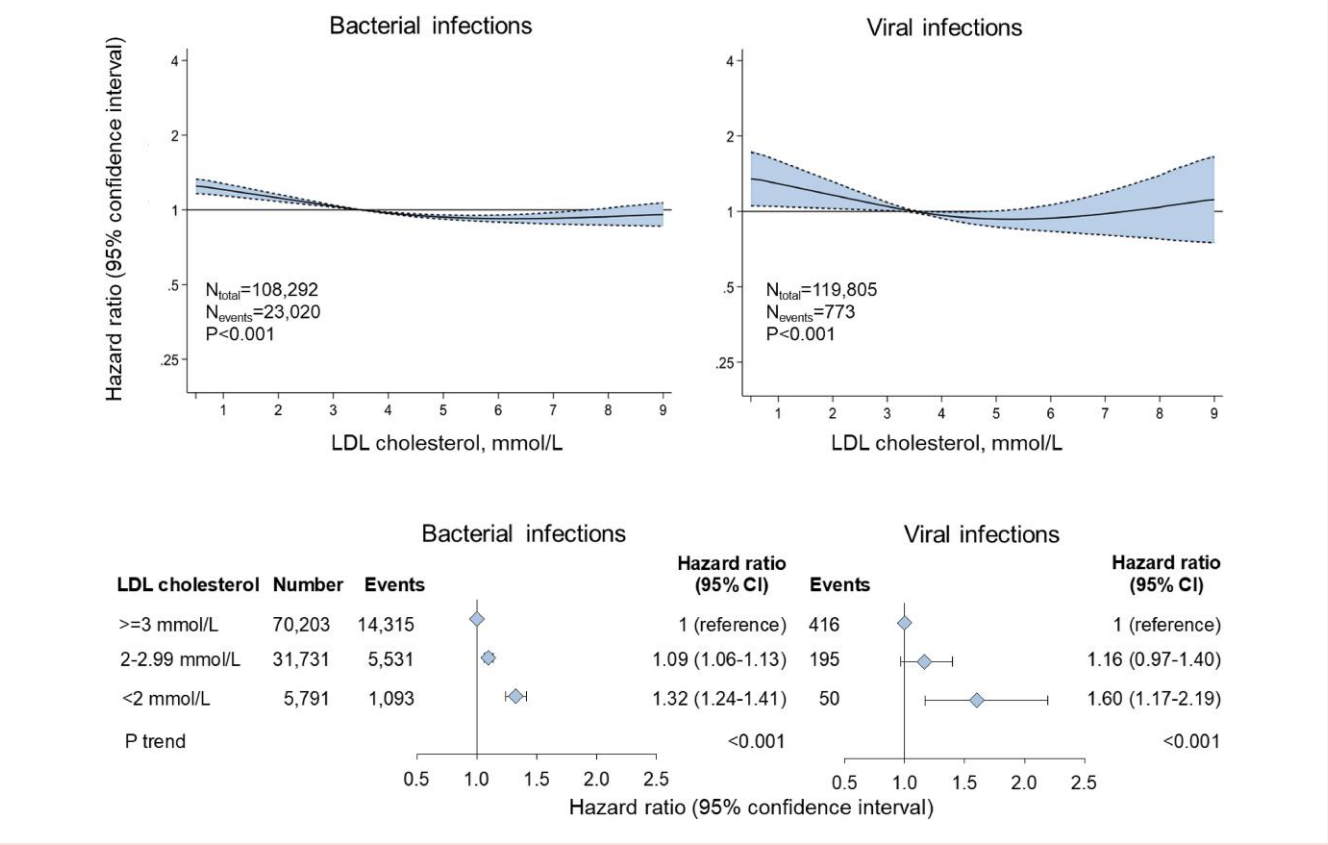


Figure 1 Observational prospective risk of hospitalization for bacterial and viral infections as a function of plasma LDL cholesterol concentration on a continuous scale in individuals in the Copenhagen general population cohorts (upper panel) and in categories of plasma LDL cholesterol (lower panel). Bacterial infections and viral infections comprised any infection with an identified agent. In the upper panel, the solid lines are the multifactorial adjusted hazard ratios and dashed lines 95% confidence intervals derived from restricted cubic spline regression. The reference is the population median for LDL cholesterol of 3.3 mmol/L. Estimates are from Cox regression analyses adjusted for age, sex, year of birth, body mass index, smoking, physical activity, alcohol consumption, education, hypertension, type 2 diabetes mellitus, and non-skin cancer and for women also menopause. *P* for trend across ordered categories (lower panel) was by the non-parametric Cuzick's extension of a Wilcoxon rank sum test. To convert mmol/L to mg/dL, multiply LDL cholesterol by 38.7. CI, confidence interval.

sepsis, and of 0.91 (0.85–0.98; $P = 0.008$) for skin infections in studies combined (*Figure 3*). Individual study estimates are shown in Supplementary material online, *Figure S5*. A 1 mmol/L lower LDL cholesterol did not have a causal effect on risk of urinary tract infections/cystitis, endocarditis, or bacterial meningitis.

Genetic low LDL cholesterol and risk of viral infections

For the *LDLR*, *HMGCR*, and *PCSK9* genetic score, a 1 mmol/L lower LDL cholesterol was associated with age- and sex-adjusted causal risk ratios of 1.15 (95% CI: 1.03–1.29; $P = 0.012$) for an unspecified viral infection and of 1.64 (1.13–2.39; $P = 0.009$) for HIV/AIDS in studies combined (*Figure 4*). Individual study estimates are shown in Supplementary material online, *Figure S6*. A 1 mmol/L lower LDL cholesterol did not have a causal effect on risk of hepatitis, viral meningitis, or viral pneumonia.

In genetic analyses using a polygenic LDL cholesterol score, a 1 mmol/L lower LDL cholesterol did not have a causal effect on risk of viral infections, HIV/AIDS hepatitis, viral meningitis, or viral pneumonia in studies combined. Individual study estimates are shown in Supplementary material online, *Figure S7*.

Genetic low LDL cholesterol and risk of ischaemic heart disease and all-cause death

As a positive control of the validity of the *LDLR*, *HMGCR*, and *PCSK9* genetic score and the polygenic LDL cholesterol score and for comparison of magnitude of risk, the causal association of the allele scores on risk of ischaemic heart disease and all-cause death[26] was included. For the *LDLR*, *HMGCR*, and *PCSK9* genetic score, a 1 mmol/L lower LDL cholesterol was associated with age- and sex-adjusted causal risk ratios of 0.60 (95% CI: 0.56–0.65; 7.4×10^{-46}) for ischaemic heart disease and 0.74 (0.57–0.95; $P = 0.017$) for all-cause death in studies combined (*Figure 4*). In genetic analyses using a polygenic LDL cholesterol score, a 1 mmol/L lower LDL cholesterol was associated with age- and sex-adjusted causal risk ratios of 0.65 (0.55–0.74; 5.0×10^{-12}) for ischaemic heart disease and 0.65 (0.58–0.74; $P = 1.5 \times 10^{-5}$) for all-cause death in studies combined. Individual study estimates are shown in Supplementary material online, *Figures S6* and *S7*.

Discussion

In the present study, we found that in observational prospective analyses, low plasma LDL cholesterol concentrations were associated

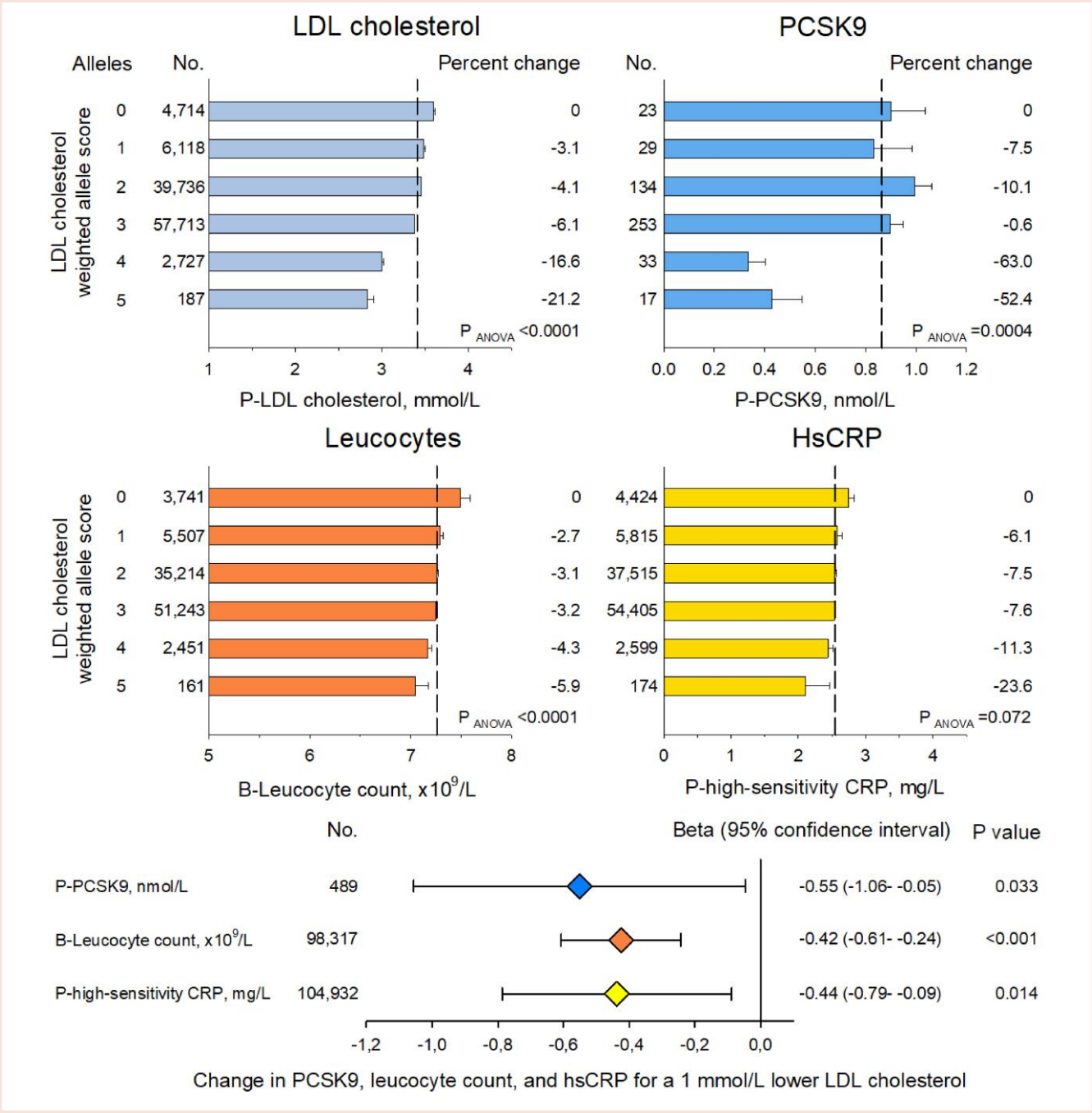


Figure 2 Plasma concentrations of LDL cholesterol, pro-protein convertase subtilisin kexin 9 (PCSK9), leucocyte count and high-sensitive C-reactive protein by a weighted LDL cholesterol allele score (upper panels) and for a 1 mmol/L genetically lower LDL cholesterol concentration by instrumental variable analysis (lower panel). *P* for trend was by Cuzick's test for trend across ordered groups. To convert LDL cholesterol from mmol/L to mg/dL, multiply by 38.7.

with high risk of bacterial and viral infections. Similar observational associations have been reported in other studies. It has been suggested that confounding by other diseases, i.e. an existing cancer, and reverse causation, as infectious diseases in the acute phase lower plasma LDL cholesterol concentrations, may contribute to these associations.[27,28] For these reasons, we examined the genetic causal effect of low LDL cholesterol on risk of infectious diseases using Mendelian randomization designs[9] in a target approach using a *LDLR*, *HMGCR*, and *PCSK9* genetic score mimicking low LDL cholesterol via statins or PCSK9 inhibitors and a polygenic LDL cholesterol score representing low LDL cholesterol in general. In causal genetic analyses, a 1 mmol/L lower LDL cholesterol resulted in a 9–12% lower risk of unspecified bacterial infections and a 6–8% lower risk of infectious diarrhoeal diseases both via the *LDLR*, *HMGCR*, and *PCSK9* genetic score and the polygenic LDL cholesterol score. The *LDLR*, *HMGCR*, and *PCSK9* genetic score also associated with a 64% higher risk of HIV/AIDS in studies combined and

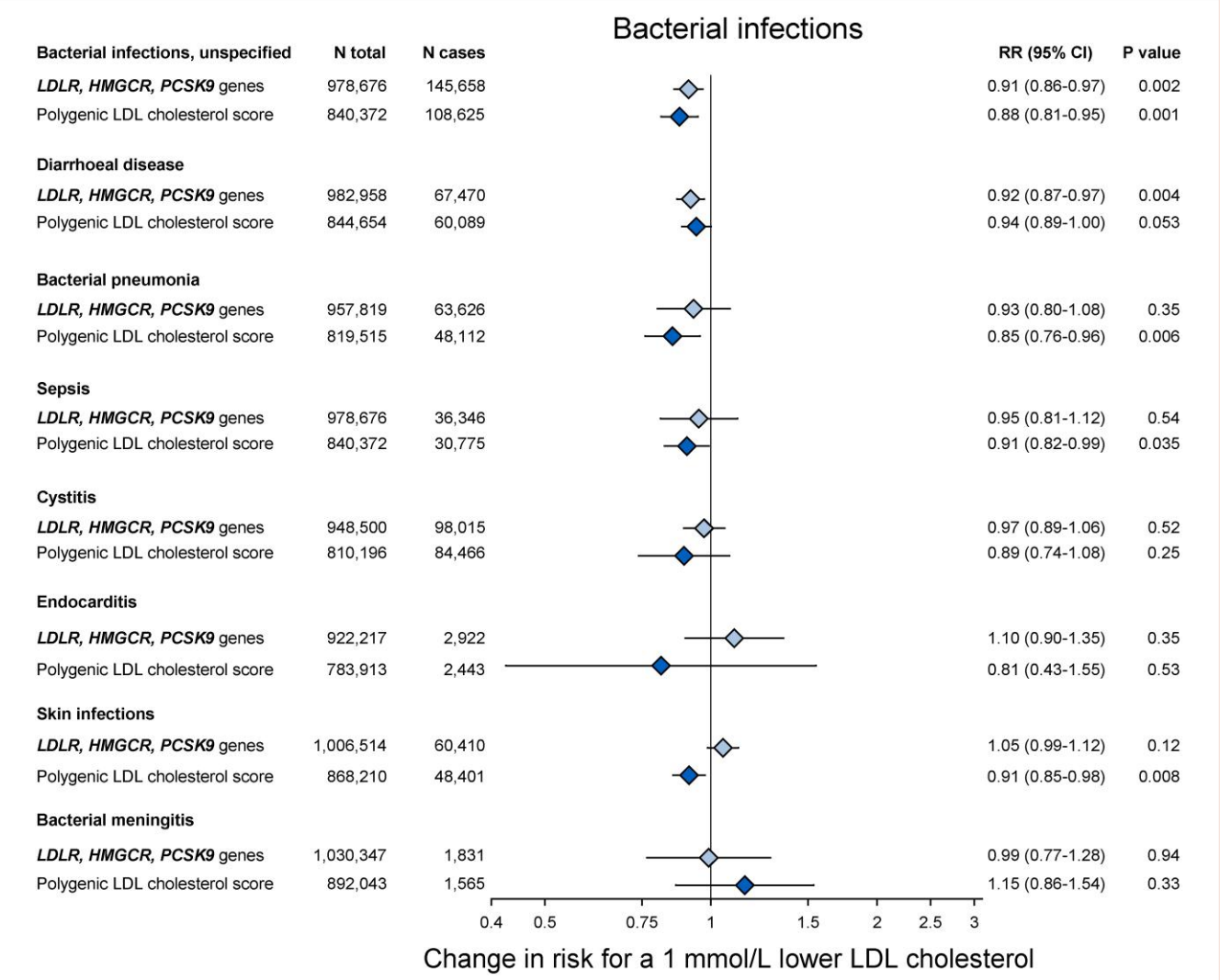


Figure 3 Mendelian randomization analyses of risk of hospitalization for bacterial infections in the Copenhagen studies, the UK Biobank, the Global Lipids Genetics Consortium/FinnGen Research Project combined for a 1 mmol/L genetically lower LDL cholesterol concentration using *LDLR*, *HMGCR*, and *PCSK9* gene score (light blue diamonds) and a polygenic LDL cholesterol score (dark blue diamonds). Individual study estimates are shown in Supplementary material online, *Figures S4* and *S5*. Estimates for the Copenhagen studies and the UK Biobank were derived from instrumental variable analyses in one-sample Mendelian randomization analysis. Estimates from the Global Lipids Genetics Consortium/FinnGen Research Project were by two-sample Mendelian randomization analyses with results reported using the inverse variance method. Estimates from the three studies were meta-analysed using a random effects model. Correcting for multiple testing using the Bonferroni method, change the level of statistical significance to 0.05/8 = 0.0063. To convert LDL cholesterol from mmol/L to mg/dL, multiply by 38.7. *N*, number; RR, risk ratio; *LDLR*, LDL receptor gene; *HMGCR*, 3-hydroxy-3-methylglutaryl-CoA gene; *PCSK9*, proprotein convertase subtilisin kexin type 9 gene; CI, confidence interval.

the polygenic LDL cholesterol score with a 15% lower risk of bacterial pneumonia, 9% lower risk of sepsis, and 9% lower risk of skin infections in studies combined. The results suggest that the effects are caused by lower LDL cholesterol in general, rather than by a specific pathway.

For comparison, a 1 mmol/L lower LDL cholesterol resulted in 35–40% lower risk of ischaemic heart disease and 26–35% lower risk of all-cause mortality.

Bacterial infections

Mechanistically, animal studies have shown that LDL particles take up toxic bacterial products such as lipopolysaccharides shredded from Gram-negative bacteria, ameliorating manifestations of experimental sepsis and infections.[3,29,30] Overexpression of PCSK9 in mice resulting in lower LDL receptor expression, reduced removal of LDL particles, and increased organ damage and inflammation during experimentally induced bacterial infections (sham surgery or caecal ligation/puncture),[31] while PCSK9 knockout mice with increased LDL receptor expression and LDL removal, and low LDL cholesterol concentrations had reduced organ damage and inflammation.[32] Jointly, this suggests that removal of LDL particles and expression of receptors normally degraded by PCSK9, e.g. the LDL receptor, potentially improves the overall response to bacterial infections.[6]

In human studies, *PCSK9* loss-of-function variants have been associated with improved survival in patients with septic shock and with a

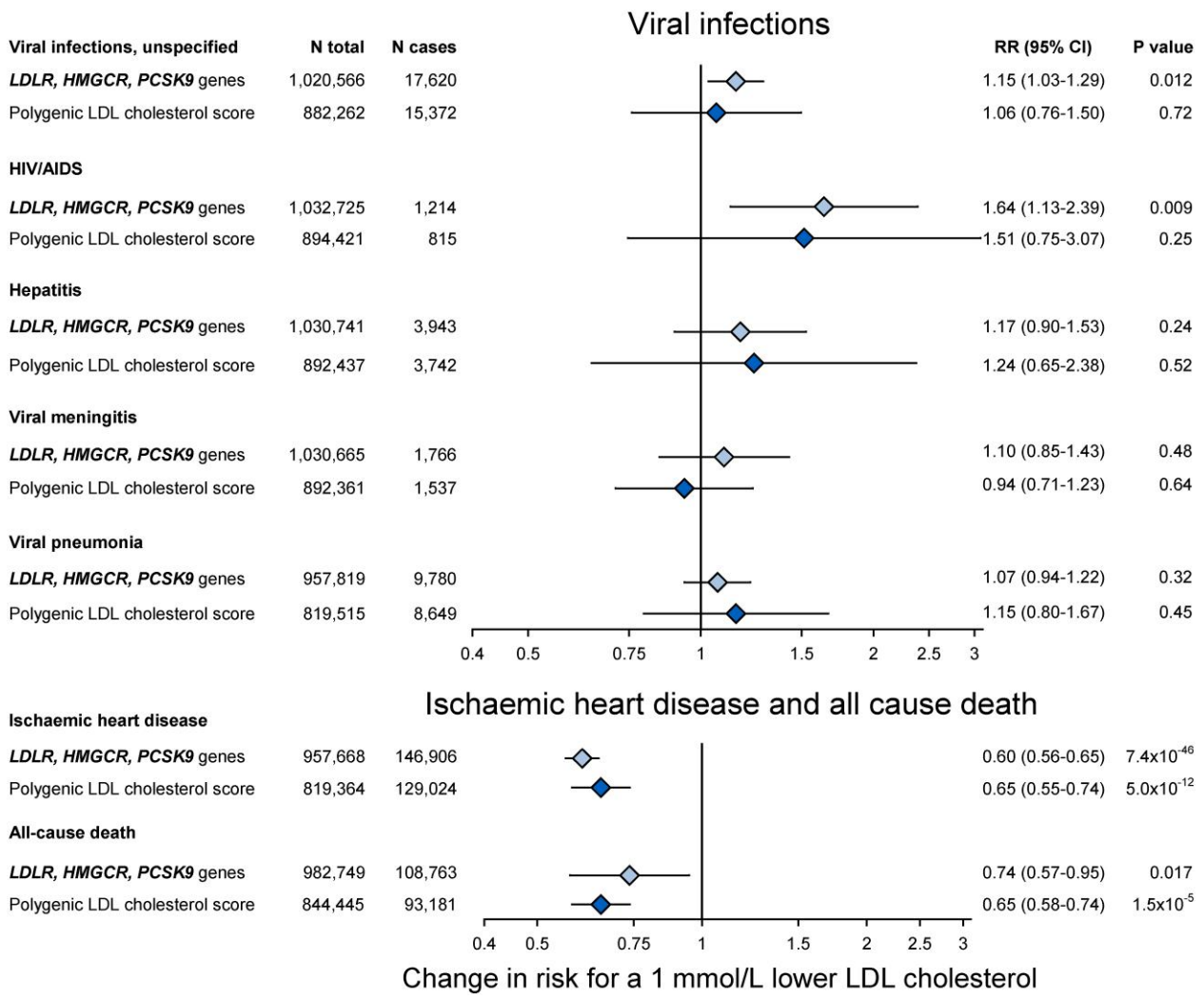


Figure 4 Mendelian randomization analyses of risk of hospitalization for viral infections in the Copenhagen studies, the UK Biobank, the Global Lipids Genetics Consortium/FinnGen Research Project combined for a 1 mmol/L genetically lower LDL cholesterol concentration using *LDLR*, *HMGCR*, and *PCSK9* gene score (light blue diamonds) and a polygenic LDL cholesterol score (dark blue diamonds). Individual study estimates are shown in Supplementary material online, *Figures S4* and *S5*. Estimates for the Copenhagen studies and the UK Biobank were derived from instrumental variable analyses in one sample analyses. Estimates from the Global Lipids Genetics Consortium/FinnGen Research Project were by two-sample Mendelian randomization analyses with results reported using the inverse variance method. Estimates from the three studies were meta-analysed using a random effects model. Correcting for multiple testing using the Bonferroni method, change the level of statistical significance to 0.05/5 = 0.01. To convert LDL cholesterol from mmol/L to mg/dL, multiply by 38.7. *N*, number; RR, risk ratio; *LDLR*, LDL receptor gene; *HMGCR*, 3-hydroxy-3-methylglutaryl-CoA gene; *PCSK9*, proprotein convertase subtilisin kexin type 9 gene; CI, confidence interval; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome.

reduced inflammatory cytokine response in patients with septic shock and in healthy volunteers after lipopolysaccharide administration.[1] In contrast to this, low plasma LDL cholesterol concentrations in observational studies have been associated with a high risk of infection and critical disease in studies of patient cohorts and prospective general population cohorts.[33–36] Some of these studies have reported a higher frequency of pre-existing co-morbidities among individuals with low plasma LDL cholesterol, indicating potential reverse causation where an infection causes the low LDL cholesterol, and confounding where a critical disease, i.e. cancer, causes both a low LDL cholesterol concentration and a high risk of infection.[36–40] This is in line with the observational findings in the present study, showing a higher risk of infection in individuals with low plasma LDL cholesterol.

Very few randomized controlled trials of lipid-lowering drugs have reported on risk of infectious disease. A meta-analysis combining eight randomized controlled trials of statins did not find an association of statin treatment with risk of infections [25 770 participants, 4035 events, relative risk 1.00 (95% CI: 0.96–1.05)] or infection-related mortality [22 260 participants, 620 events, relative risk 0.97 (0.83–1.13)] compared to placebo.[41] These studies did not include information on type of infection.[41] The lack of an association might be due to the short treatment duration in clinical trials compared to the lifelong effect of

lower LDL cholesterol in genetic studies. A meta-analysis of 14 PCSK9 inhibitor randomized controlled trials have shown a higher rate of upper respiratory tract infection signs and symptoms in patients receiving alirocumab compared to placebo [5234 participants, hazard ratio 1.87 (1.04–3.38)][42]; however, it is not known if this is a side effect of alirocumab rather than caused by a lowering of LDL cholesterol *per se*. A planned randomized placebo-controlled double-blind trial will assess the difference in survival after 28 days in patients with sepsis or septic shock, treated with alirocumab or placebo in an intensive care unit (NCT03634293).

A Mendelian randomization study using the UK Biobank examined a polygenic risk score for LDL cholesterol and found no effect of higher concentrations of LDL cholesterol on risk of hospitalization for any infection (bacterial and viral combined), antibiotic use, or 28 days survival after sepsis [407 558 participants, 29 600 events, relative risk 1.01 (95% CI: 0.97–1.05)].[40] Similar results were found in a Mendelian randomization study of a patient cohort [7804 participants; odds ratio (OR) for sepsis 1.02 (0.97–1.07); for intensive care unit admission 1.01 (0.95–1.07); and for in-hospital death 0.92 (0.81–1.05)].[36] In contrast to this, two-sample Mendelian randomization studies using the GLGC and UK Biobank data found a reduced risk of sepsis with an OR of 0.72 (0.57–0.90) for a 1 mmol/L lower LDL cholesterol in individuals younger than 75 years[43] and borderline increased risk of sepsis with an OR of 1.10 (0.99–1.24) for a 1 mmol/L higher LDL cholesterol.[44] These studies did not examine other specific types of infections and are not directly comparable to our results.

Taken together, both animal and human experimental studies support a beneficial effect of low LDL cholesterol on risk of bacterial infections in line with the causal genetic results of the present study. Randomized controlled trials and previous Mendelian randomization studies pooling bacterial and viral infections have shown no causal effect of LDL cholesterol on infection risk. The reduced risk of unspecified bacterial infection and infectious diarrhoeal disease observed in the present study may be caused by increased removal of lipopolysaccharides as suggested in experimental studies; however, a lower inflammatory burden as seen by the lower concentrations of C-reactive protein and leucocyte count in the present study and that well-perfused (non-atherosclerotic) tissues and organs form better barriers against bacteria compared to an intestine with a reduced perfusion may also contribute.

Viral infections

Virus requires several molecules for virus attachment, cell entry, replication, and virion release. Some viruses can bind directly to the LDL and VLDL receptors[6] and be taken up into host cells and thus facilitate replication.[4,5] In cell studies, hepatitis B and C virus, rhinovirus, Japanese encephalitis virus, and vesicular stomatitis virus have been shown to use LDL receptors and other LDL receptor family members for cell binding and entry.[45–47] There is some evidence from cell studies that PCSK9 might influence hepatitis C virus infectivity, as it down-regulates the LDL and VLDL receptors.[5,48] Theoretically, this means that PCSK9 inhibition might facilitate hepatitis C virus uptake into hepatocytes, although results are conflicting.[49]

Human immunodeficiency virus is a retrovirus with surface envelope glycoproteins facilitating viral attachment and entry into T helper cells, monocytes, macrophages, and dendritic cells. During binding to host cells, the virus envelope fuses with the host cell membrane, incorporating CD81 and CD63 into the virus membrane and expressing these proteins on the cell surface after the fusion.[50] Both CD81 and CD63 are targets for degradation by PCSK9[4,5]; however, it is unclear if this might increase susceptibility to HIV infection and how such a susceptibility may be mediated.

Analysis of 14 observational studies pooling data from 19 988 patients with COVID-19 showed that use of statins reduced risk of adverse outcomes by 49% [OR 0.51 (95% CI: 0.41–0.63)].[51] Several Mendelian randomization studies have examined the effect of LDL cholesterol on risk of hospitalization for COVID-19. One study found that a one standard deviation (0.87 mmol/L) higher LDL cholesterol increased risk of COVID-19 by 58% [387 079 participants and 1211 events; OR 1.58 (1.21–2.06)].[52] Another study found that a 1 mmol/L higher LDL cholesterol increased risk of COVID-19 with an OR of 1.11 (1.0–1.23).[53]

Taken together, cell studies show that many viruses—including human immunodeficiency virus—use LDL and VLDL receptors for cell entry; however, it is unclear whether increasing the number of receptors by lipid-lowering treatment with statins or PCSK9 inhibitors might increase risk of virus uptake and propagation. The present study suggests that genetically low LDL cholesterol may increase risk of hospitalization for an HIV infection. This risk contrasts with the large reduction in risk of ischaemic heart disease and all-cause death also shown in the present study. People with HIV in anti-viral treatment often have dyslipidaemia caused by the treatment. In these individuals, both statins[54] and PCSK9 inhibitors[55] have been shown to lower risk of cardiovascular disease.

Limitations

Infection with bacteria or viruses requires exposure to the specific agents and may be associated with a specific geographical location and potentially also a certain behaviour for transmission. Hospitalization for an infectious disease also requires the disease to be of some severity and potentially that co-morbidities are present. This may be a limitation of the present study, using hospital diagnoses in populations from Western and Northern European countries. This also limits the spectrum of infectious diseases examined to diseases present in these areas. Individuals with less severe disease may not have been hospitalized, and some diseases cannot be examined due to a low number of cases. Also, using register data to define infectious disease, endpoints have limitations, as not all cases of endocarditis, infectious diarrhoeal disease, and sepsis are caused by bacterial infections; and many disease agents are not easily adjudicated. The Mendelian randomization design has three assumptions,[9] all addressed in the present study: (i) the genotypes used as instruments were associated with low LDL cholesterol, as shown in *Figure 2*; (ii) the genotypes should be associated with the risk of infectious diseases through LDL cholesterol, as verified using the MR Egger test for pleiotropic effects; and (iii) the genotypes were independent of other factors affecting the outcome, as shown in Supplementary material online, *Figure S3*. These findings support the validity of the Mendelian randomization results.

Conclusion

Genetically low LDL cholesterol concentrations were associated with lower concentration of markers of inflammation; lower risk of hospitalization for unspecified bacterial infections, infectious diarrhoeal diseases, bacterial pneumonia, and sepsis; and higher risk of viral infections and HIV/AIDS.

Data availability

Due to Danish legislation, the data that support this study cannot be made publicly available. Additional analyses can be performed upon a reasonable request to the corresponding author.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Acknowledgements

We are indebted to the participants and staff of the Copenhagen General Population Study and the Copenhagen City Heart Study. We also thank the participants of the UK Biobank study,[10] the Global Lipids Genetics Consortium (GLGC),[11] the FinnGen Research Project, and the consortia for making their data publicly available.

Funding

This work was supported by the Copenhagen University Hospital—Rigshospitalet and Copenhagen University Hospital—Herlev and Gentofte. The funding sources had no role in the study design, collection of data, writing of the report, or decision to submit the article for publication.

Conflict of interest: None declared.

References

1. Walley KR, Thain KR, Russell JA, Reilly MP, Meyer NJ, Ferguson JF, Christie JD, Nakada T-A, Fjell CD, Thair SA, Cirstea MS, Boyd JH. PCSK9 is a critical regulator of the innate immune response and septic shock outcome. *Sci Transl Med* 2014;**6**:258ra143.
2. Walley KR, Francis GA, Opal SM, Stein EA, Russell JA, Boyd JH. The central role of proprotein convertase subtilisin/kexin type 9 in septic pathogen lipid transport and clearance. *Am J Respir Crit Care Med* 2015;**192**:1275–1286.
3. Van Amersfoort ES, Van Berkel TJ, Kuiper J. Receptors, mediators, and mechanisms involved in bacterial sepsis and septic shock. *Clin Microbiol Rev* 2003;**16**:379–414.
4. Agnello V, Abel G, Elfahal M, Knight GB, Zhang QX. Hepatitis C virus and other flaviviridae viruses enter cells via low density lipoprotein receptor. *Proc Natl Acad Sci U S A* 1999;**96**:12766–12771.
5. Kumar A, Hossain RA, Yost SA, Bu W, Wang Y, Dearborn AD, Grakoui A, Cohen JI, Marcotrigiano J. Structural insights into hepatitis C virus receptor binding and entry. *Nature* 2021;**598**:521–525.
6. Seidah NG, Garcon D. Expanding biology of PCSK9: roles in atherosclerosis and beyond. *Curr Atheroscler Rep* 2022;**24**:821–830.
7. Ference BA, Ray KK, Catapano AL, Ference TB, Burgess S, Neff DR, Oliver-Williams C, Wood AM, Butterworth AS, Di Angelantonio E, Danesh J, Kastelein JJP, Nicholls SJ. Mendelian randomization study of ACLY and cardiovascular disease. *N Engl J Med* 2019;**380**:1033–1042.
8. Benn M, Nordestgaard BG. From genome-wide association studies to Mendelian randomization: novel opportunities for understanding cardiovascular disease causality, pathogenesis, prevention, and treatment. *Cardiovasc Res* 2018;**114**:1192–1208.
9. Burgess S, Timpson NJ, Ebrahim S, Smith GD. Mendelian randomization: where are we now and where are we going? *Int J Epidemiol* 2015;**44**:379–388.
10. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, Motyer A, Vukcevic D, Delaneau O, O'Connell J, Cortes A, Welsh S, Young A, Effingham M, McVean G, Leslie S, Allen N, Donnelly P, Marchini J. The UK Biobank resource with deep phenotyping and genomic data. *Nature* 2018;**562**:203–209.
11. Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, Buchkovich ML, Mora S, Beckmann JS, Bragg-Gresham JL, Chang H-Y, Demirkan A, Hertog HMD, Do R, Donnelly LA, Ehret GB, Esko T, Feitosa MF, Ferreira T, Fischer K, Fontanillas P, Fraser RM, Freitag DF, Gurdasani D, Heikkilä K, Hyppönen E, Isaacs A, Jackson AU, Johansson Å, Johnson T, Kaakinen M, Kettunen J, Kleber ME, Li X, Luan J, Lyytikäinen L-P, Magnusson PKE, Mangino M, Mihailov E, Montasser ME, Müller-Nurasyid M, Nolte IM, O'Connell JR, Palmer CD, Perola M, Petersen A-K, Sanna S, Saxena R, Service SK, Shah S, Shungin D, Sidore C, Song C, Strawbridge RJ, Surakka I, Tanaka T, Teslovich TM, Thorleifsson G, Van den Herik EG, Voight BF, Volcik KA, Waite LL, Wong A, Wu Y, Zhang W, Absher D, Asiki G, Barroso I, Been LF, Bolton JL, Bonnycastle LL, Brambilla P, Burnett MS, Cesana G, Dimitriou M, Doney ASF, Döring A, Elliott P, Epstein SE, Eyjolfsson GI, Gigante B, Goodarzi MO, Grallert H, Gravito ML, Groves CJ, Hallmans G, Hartikainen A-L, Hayward C, Hernandez D, Hicks AA, Holm H, Hung Y-J, Illig T, Jones MR, Kaleebu P, Kastelein JJP, Khaw K-T, Kim E, Klopp N, Komulainen P, Kumari M, Langenberg C, Lehtimäki T, Lin S-Y, Lindström J, Loos RJF, Mach F, McArdle WL, Meisinger C, Mitchell BD, Müller G, Nagaraja R, Narisu N, Nieminen TVM, Nsubuga RN, Olafsson I, Ong KK, Palotie A, Papamarkou T, Pomilla C, Pouta A, Rader DJ, Reilly MP, Ridker PM, Rivadeneira F, Rudan I, Ruokonen A, Samani N, Scharnagl H, Seeley J, Silander K, Stančáková A, Stirrups K, Swift AJ, Tiret L, Uitterlinden AG, van Pelt LJ, Vedantam S, Wainwright N, Wijmenga C, Wild SH, Willemsen G, Wilsgaard T, Wilson JF, Young EH, Zhao JH, Adair LS, Arveiler D, Assimes TL, Bandinelli S, Bennett F, Bochud M, Boehm BO, Boomsma DI, Borecki IB, Bornstein SR, Bovet P, Burnier M, Campbell H, Chakravarti A, Chambers JC, Chen Y-DI, Collins FS, Cooper RS, Danesh J, Dedoussis G, de Faire U, Feranil AB, Ferrières J, Ferrucci L, Freimer NB, Gieger C, Groop LC, Gudnason V, Gyllensten U, Hamsten A, Harris TB, Hingorani A, Hirschhorn JN, Hofman A, Hovingh GK, Hsiung CA, Humphries SE, Hunt SC, Hveem K, Iribarren C, Järvelin M-R, Jula A, Kähönen M, Kaprio J, Kesäniemi A, Kivimaki M, Kooner JS, Koudstaal PJ, Krauss RM, Kuh D, Kuusisto J, Kyvik KO, Laakso M, Lakka TA, Lind L, Lindgren CM, Martin NG, März W, McCarthy MI, McKenzie CA, Meneton P, Metspalu A, Moilanen L, Morris AD, Munroe BP, Njølstad I, Pedersen NL, Power C, Pramstaller PP, Price JF, Psaty BM, Quertermous T, Rauramaa R, Saleheen D, Salomaa V, Sanghera DK, Saramies J, Schwarz PEH, Sheu WHH, Shuldiner AR, Siegbahn A, Spector TD, Stefansson K, Strachan DP, Tayo BO, Tremoli E, Tuomilehto J, Uusitupa M, van Duijn CM, Vollenweider P, Wallentin L, Wareham NJ, Whitfield JB, Wolffenbuttel BHR, Ordovas JM, Boerwinkle E, Palmer CNA, Thorsteinsdottir U, Chasman DI, Rotter JI, Franks PW, Ripatti S, Cupples LA, Sandhu MS, Rich SS, Boehnke M, Deloukas P, Kathiresan S, Mohlke KL, Ingelsson E, Abecasis GR; Global Lipids Genetics Consortium Discovery and refinement of loci associated with lipid levels. *Nat Genet* 2013;**45**:1274–1283.
12. Benn M, Nordestgaard BG, Frikke-Schmidt R, Tybjaerg-Hansen A. Low LDL cholesterol, PCSK9 and HMGCR genetic variation, and risk of Alzheimer's disease and Parkinson's disease: Mendelian randomisation study. *BMJ* 2017;**357**:j1648.
13. Kathiresan S, Melander O, Guiducci C, Surti A, Burtt NP, Rieder MJ, Cooper GM, Roos C, Voight BF, Havulinna AS, Wahlstrand B, Hedner T, Corella D, Tai ES, Ordovas JM, Berglund G, Vartiainen E, Jousilahti P, Hedblad B, Taskinen M-R, Newton-Cheh C, Salomaa V, Peltonen L, Groop L, Altshuler DM, Orho-Melander M. Six new loci associated with blood low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides in humans. *Nat Genet* 2008;**40**:189–197.
14. Kurki MI, Karjalainen J, Palta P, Sipila TP, Kristiansson K, Donner KM, Reeve MP, Laivuori H, Aavikko M, Kaunisto MA, Loukola A, Lahtela E, Mattsson H, Laiho P, Parolo PDB, Lehisto AA, Kanai M, Mars N, Rämö J, Kiiskinen T, Heyne HO, Veerapen K, Rüeger S, Lemmelä S, Zhou W, Ruotsalainen S, Pärn K, Hiekkalinna T, Koskelainen S, Paajanen T, Llorens V, Gracia-Tabuenca J, Siirtola H, Reis K, Elnahas AG, Sun B, Foley CN, Aalto-Setälä K, Alasoo K, Arvas M, Auro K, Biswas S, Bizaki-Vallaskangas A, Carpen O, Chen C-Y, Dada AO, Ding Z, Ehm MG, Eklund K, Färkkilä M, Finucane H, Ganna A, Ghazal A, Graham RR, Green EM, Hakanen A, Hautalahti M, Hedman ÅK, Hiltunen M, Hinttala R, Hovatta I, Hu X, Huertas-Vazquez A, Huilaja L, Hunkapiller J, Jacob H, Jensen J-N, Joensuu H, John S, Julkunen V, Jung M, Junttila J, Kaarniranta K, Kähönen M, Kajanne R, Kallio L, Kälviäinen R, Kaprio J, Gen F, Kerimov N, Kettunen J, Kilpeläinen E, Kilpi T, Klinger K, Kosma V-M, Kuopio T, Kurra V, Laisk T, Laukkanen J, Lawless N, Liu A, Longerich S, Mägi R, Mäkelä J, Mäkitie A, Malarstig A, Mannermaa A, Maranville J, Matakidou A, Meretoja T, Mozaffari SV, Niemi MEK, Niemi M, Niiranen T, Donnell CJO, Obeidat ME, Okafo G, Ollila HM, Palomäki A, Palotie T, Partanen J, Paul DS, Pelkonen M, Pendergrass RK, Petrovski S, Pitkäranta A, Platt A, Pulford D, Punkka E, Pussinen P, Raghavan N, Rahimov F, Rajpal D, Renaud NA, Riley-Gillis B, Rodosthenous R, Saarentaus E, Salminen A, Salminen E, Salomaa V, Schleutker J, Serpi R, Shen H-Y, Siegel R, Silander K, Siltanen S, Soini S, Soininen H, Sul JH, Tachmazidou I, Tasanen K, Tienari P, Toppila-Salmi S, Tukiainen T, Tuomi T, Turunen JA, Ulirsch JC, Vaura F, Virolainen P, Waring J, Waterworth D, Yang R, Nelis M, Reigo A, Metspalu A, Milani L, Esko T, Fox C, Havulinna AS, Perola M, Ripatti S, Jalanko A, Laitinen T, Mäkelä TP, Plenge R, McCarthy M, Runz H, Daly MJ, Palotie A. FinnGen provides genetic insights from a well-phenotyped isolated population. *Nature* 2023;**613**:508–518.
15. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;**39**:30–33.
16. Benfield T, Jensen JS, Nordestgaard BG. Influence of diabetes and hyperglycaemia on infectious disease hospitalisation and outcome. *Diabetologia* 2007;**50**:549–554.
17. Voight BF, Kang HM, Ding J, Palmer CD, Sidore C, Chines PS, Burtt NP, Fuchsberger C, Li Y, Erdmann J, Frayling TM, Heid IM, Jackson AU, Johnson T, Kilpeläinen TO, Lindgren CM, Morris AP, Prokopenko I, Randall JC, Saxena R, Soranzo N, Speliotes EK, Teslovich TM, Wheeler E, Maguire J, Parkin M, Potter S, Rayner NW, Robertson N, Stirrups K, Winckler W, Sanna S, Mulas A, Nagaraja R, Cucca F, Barroso I, Deloukas P, Loos RJF, Kathiresan S, Munroe PB, Newton-Cheh C, Pfeufer A, Samani NJ, Schunkert H, Hirschhorn JN, Altshuler D, McCarthy MI, Abecasis GR, Boehnke M. The metabochip, a custom genotyping array for genetic studies of metabolic, cardiovascular, and anthropometric traits. *PLoS Genet* 2012;**8**:e1002793.
18. Emanuelsson F, Marott S, Tybjaerg-Hansen A, Nordestgaard BG, Benn M. Impact of glucose level on micro- and macrovascular disease in the general population: a Mendelian randomization study. *Diabetes Care* 2020;**43**:894–902.
19. Akaike H. Information theory and an extension of the maximum likelihood principle. In: Parzen E TK, Kitagawa G, ed. *Selected Papers of Hirotugu Akaike*. New York, USA: Springer; 1998, p 199–213.
20. Baum C, Schaffer M, Stillman S. Instrumental variables and GMM: estimation and testing. *Stata J* 2003;**3**:1–31.
21. Burgess S, Bowden J, Fall T, Ingelsson E, Thompson SG. Sensitivity analyses for robust causal inference from Mendelian randomization analyses with multiple genetic variants. *Epidemiology* 2017;**28**:30–42.
22. Sargan JD. The estimation of economic relationships using instrumental variables. *Econometrica* 1958;**26**:393–415.

23. Consortium CAD, Deloukas P, Kanoni S, Willenborg C, Farrall M, Assimes TL, Thompson JR, Ingelsson E, Saleheen D, Erdmann J, Goldstein BA, Stirrups K, König IR, Cazier J-B, Johansson A, Hall AS, Lee J-Y, Willer CJ, Chambers JC, Esko T, Folkersen L, Goel A, Grundberg E, Havulinna AS, Ho WK, Hopewell JC, Eriksson N, Kleber ME, Kristiansson K, Lundmark P, Lyytikäinen L-P, Rafelt S, Shungin D, Strawbridge RJ, Thorleifsson G, Tikkanen E, Van Zuydam N, Voight BF, Waite LL, Zhang W, Ziegler A, Absher D, Altshuler D, Balmforth AJ, Barroso I, Braund PS, Burgdorf C, Claudi-Boehm S, Cox D, Dimitriou M, Do R; DIAGRAM Consortium; CARDIOGENICS Consortium; Doney ASF, El Mokhtari NE, Eriksson P, Fischer K, Fontanillas P, Franco-Cereceda A, Gigante B, Groop L, Gustafsson S, Hager J, Hallmans G, Han B-G, Hunt SE, Kang HM, Illig T, Kessler T, Knowles JW, Kolovou G, Kuusisto J, Langenberg C, Langford C, Leander K, Lokki M-L, Lundmark A, McCarthy MI, Meisinger C, Melander O, Mihailov E, Maouche S, Morris AD, Müller-Nurasyid M, MuTHER Consortium; Nikus K, Peden JF, Rayner NW, Rasheed A, Rosinger S, Rubin D, Rumpf MP, Schäfer A, Sivananthan M, Song C, Stewart AFR, Tan S-T, Thorgeirsson G, van der Schoot CE, Wagner PJ; Wellcome Trust Case Control Consortium; Wells GA, Wild PS, Yang T-P, Amouyel P, Arveiler D, Basart H, Boehnke M, Boerwinkle E, Brambilla P, Cambien F, Cupples AL, de Faire U, Dehghan A, Diemert P, Epstein SE, Evans A, Ferrario MM, Ferrières J, Gauguier D, Go AS, Goodall AH, Gudnason V, Hazen SL, Holm H, Iribarren C, Jang Y, Kähönen M, Kee D, Kim H-S, Klopp N, Koenig W, Kratzer W, Kuulasmaa K, Laakso M, Laaksonen R, Lee J-Y, Lind L, Ouwehand WH, Parish S, Park JE, Pedersen NL, Peters A, Quertermous T, Rader DJ, Salomaa V, Schadt E, Shah SH, Sinisalo J, Stark K, Stefansson K, Trégouët D-A, Virtamo J, Wallentin L, Wareham N, Zimmermann ME, Nieminen MS, Hengstenberg C, Sandhu MS, Pastinen T, Syvänen A-C, Hovingh GK, Dedoussis G, Franks PW, Lehtimäki T, Metspalu A, Zalloua PA, Siegbahn A, Schreiber S, Ripatti S, Blankenberg SS, Perola M, Clarke R, Boehm BO, O'Donnell C, Reilly MP, März W, Collins R, Kathiresan S, Hamsten A, Kooner JS, Thorsteinsdottir U, Danesh J, Palmer CNA, Roberts R, Watkins H, Schunkert H, Samani NJ. Large-scale association analysis identifies new risk loci for coronary artery disease. *Nat Genet* 2013;**45**:25–33.
24. Nichols A. *IVPOIS: Stata module to estimate an instrumental variables Poisson regression via GMM*. Statistical Software Components S456890, Boston College Department of Economics; 2007. Date revised 03 September 2008.
25. Bonferroni CE. Teoria statistica delle classi e calcolo delle probabilità. In: *Firenze, Italy: Pubblicazioni del R Istituto Superiore di Scienze Economiche e Commerciali di Firenze*; 1936.
26. Benn M, Nordestgaard BG, Grande P, Schnohr P, Tybjaerg-Hansen A. PCSK9 R46L, low-density lipoprotein cholesterol levels, and risk of ischemic heart disease: 3 independent studies and meta-analyses. *J Am Coll Cardiol* 2010;**55**:2833–2842.
27. Iribarren C, Jacobs DR Jr., Sidney S, Claxton AJ, Feingold KR. Cohort study of serum total cholesterol and in-hospital incidence of infectious diseases. *Epidemiol Infect* 1998;**121**:335–347.
28. Chidambaram V, Geetha HS, Kumar A, Majella MG, Sivakumar RK, Voruganti D, Mehta JL, Karakousis PC. Association of lipid levels with COVID-19 infection, disease severity and mortality: a systematic review and meta-analysis. *Front Cardiovasc Med* 2022;**9**:862999.
29. Netea MG, Demacker PN, Kullberg BJ, Boerman OC, Verschueren I, Stalenhoef AF, van deer Meer JW. Low-density lipoprotein receptor-deficient mice are protected against lethal endotoxemia and severe gram-negative infections. *J Clin Invest* 1996;**97**:1366–1372.
30. Bhakdi S, Tranum-Jensen J, Utermann G, Fussle R. Binding and partial inactivation of Staphylococcus aureus alpha-toxin by human plasma low density lipoprotein. *J Biol Chem* 1983;**258**:5899–5904.
31. Yuan Y, Wu W, Sun S, Zhang Y, Chen Z. PCSK9: a potential therapeutic target for sepsis. *J Immunol Res* 2020;**2020**:2687692.
32. Dwivedi DJ, Grin PM, Khan M, Prat A, Zhou J, Fox-Robichaud AE, Seidah NG, Liaw PC. Differential expression of PCSK9 modulates infection, inflammation, and coagulation in a murine model of sepsis. *Shock* 2016;**46**:672–680.
33. Shor R, Wainstein J, Oz D, Boaz M, Matas Z, Fux A, Halabe A. Low serum LDL cholesterol levels and the risk of fever, sepsis, and malignancy. *Ann Clin Lab Sci* 2007;**37**:343–348.
34. Lagrost L, Girard C, Grosjean S, Masson D, Deckert V, Gautier T, Debomy F, Vinault S, Jeannin A, Labbé J, Bonithon-Kopp C. Low preoperative cholesterol level is a risk factor of sepsis and poor clinical outcome in patients undergoing cardiac surgery with cardiopulmonary bypass. *Crit Care Med* 2014;**42**:1065–1073.
35. Chien YF, Chen CY, Hsu CL, Chen KY, Yu CJ. Decreased serum level of lipoprotein cholesterol is a poor prognostic factor for patients with severe community-acquired pneumonia that required intensive care unit admission. *J Crit Care* 2015;**30**:506–510.
36. Feng Q, Wei WQ, Chaugai S, Leon BGC, Mosley JD, Leon DAC, Jiang L, Ihegword A, Shaffer CM, Linton MF, Chung CP, Stein CM. Association between low-density lipoprotein cholesterol levels and risk for sepsis among patients admitted to the hospital with infection. *JAMA Netw Open* 2019;**2**:e187223.
37. Khovidhunkit W, Kim MS, Memon RA, Shigenaga JK, Moser AH, Feingold KR, Grunfeld C. Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. *J Lipid Res* 2004;**45**:1169–1196.
38. Kaysen GA, Grimes B, Dalrymple LS, Chertow GM, Ishida JH, Delgado C, Segal M, Chiang J, Dwyer T, Johansen KL. Associations of lipoproteins with cardiovascular and infection-related outcomes in patients receiving hemodialysis. *J Clin Lipidol* 2018;**12**:481–487.e14.
39. Kaysen GA, Ye X, Raimann JG, Wang Y, Topping A, Usvyat LA, Stuard S, Canaud B, van der Sande FM, Kooman JP, Kotanko P; Monitoring Dialysis Outcomes (MONDO) Initiative. Lipid levels are inversely associated with infectious and all-cause mortality: international MONDO study results. *J Lipid Res* 2018;**59**:1519–1528.
40. Trinder M, Walley KR, Boyd JH, Brunham LR. Causal inference for genetically determined levels of high-density lipoprotein cholesterol and risk of infectious disease. *Arterioscler Thromb Vasc Biol* 2020;**40**:267–278.
41. van den Hoek HL, Bos WJ, de Boer A, van de Garde EM. Statins and prevention of infections: systematic review and meta-analysis of data from large randomised placebo controlled trials. *BMJ* 2011;**343**:d7281.
42. Jones PH, Bays HE, Chaudhari U, Pordy R, Lorenzato C, Miller K, Robinson JG. Safety of alirocumab (a PCSK9 monoclonal antibody) from 14 randomized trials. *Am J Cardiol* 2016;**118**:1805–1811.
43. Zhang K, Liu W, Liang H. Effect of statins on sepsis and inflammatory factors: a Mendelian randomization study. *Eur J Clin Invest* 2024;**54**:e14164.
44. Chen J, Chen W, Wu L, Wang RH, Xiang JJ, Zheng FK, Huang QM. Causal relationships between plasma lipids and sepsis: a Mendelian randomization study. *Medicine (Baltimore)* 2023;**102**:e36288.
45. Huang L, Li H, Ye Z, Xu Q, Fu Q, Sun W, Qi W, Yue J. Berbamine inhibits Japanese encephalitis virus (JEV) infection by compromising TPRMLs-mediated endolysosomal trafficking of low-density lipoprotein receptor (LDLR). *Emerg Microbes Infect* 2021;**10**:1257–1271.
46. Hofer F, Gruenberger M, Kowalski H, Machat H, Huettinger M, Kuechler E, Blaas D. Members of the low density lipoprotein receptor family mediate cell entry of a minor-group common cold virus. *Proc Natl Acad Sci U S A* 1994;**91**:1839–1842.
47. Li Y, Luo G. Human low-density lipoprotein receptor plays an important role in hepatitis B virus infection. *PLoS Pathog* 2021;**17**:e1009722.
48. Zeisel MB, Da Costa D, Baumert TF. Opening the door for hepatitis C virus infection in genetically humanized mice. *Hepatology* 2011;**54**:1873–1875.
49. Ramanathan A, Gusarova V, Stahl N, Gurnett-Bander A, Kyratsous CA. Alirocumab, a therapeutic human antibody to PCSK9, does not affect CD81 levels or hepatitis C virus entry and replication into hepatocytes. *PLoS One* 2016;**11**:e0154498.
50. Florin L, Lang T. Tetraspanin assemblies in virus infection. *Front Immunol* 2018;**9**:1140.
51. Pal R, Banerjee M, Yadav U, Bhattacharjee S. Statin use and clinical outcomes in patients with COVID-19: an updated systematic review and meta-analysis. *Postgrad Med J* 2022;**98**:354–359.
52. Aung N, Khanji MY, Munroe PB, Petersen SE. Causal inference for genetic obesity, cardiometabolic profile and COVID-19 susceptibility: a Mendelian randomization study. *Front Genet* 2020;**11**:586308.
53. Zhang K, Dong SS, Guo Y, Tang SH, Wu H, Yao S, Wang P-F, Zhang K, Xue H-Z, Huang W, Ding J, Yang T-L. Causal associations between blood lipids and COVID-19 risk: a two-sample Mendelian randomization study. *Arterioscler Thromb Vasc Biol* 2021;**41**:2802–2810.
54. Grinspoon SK, Fitch KV, Zanni MV, Fichtenbaum CJ, Umbleja T, Aberg JA, Overton ET, Malvestutto CD, Bloomfield GS, Currier JS, Martinez E, Roa JC, Diggs MR, Fulda ES, Paradis K, Wiviott SD, Foldyna B, Looby SE, Desvigne-Nickens P, Alston-Smith B, Leon-Cruz J, McCallum S, Hoffmann U, Lu MT, Ribaudo JH, Douglas PS; REPRIEVE Investigators. Pitavastatin to prevent cardiovascular disease in HIV infection. *N Engl J Med* 2023;**389**:687–699.
55. Boccara F, Kumar PN, Caramelli B, Calmy A, Lopez JAG, Bray S, Cyrille M, Rosenson RS, BEIJERINCK Investigators. Evolocumab in HIV-infected patients with dyslipidemia: primary results of the randomized, double-blind BEIJERINCK study. *J Am Coll Cardiol* 2020;**75**:2570–2584.