GWAS Identifies *LINC01184/SLC12A2* as a Risk Locus for Skin and Soft Tissue Infections

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TO THE EDITOR

Microbial invasion of the skin and underlying soft tissues, known as skin and soft tissue infections (SSTIs), contribute to a considerable burden of disease worldwide (Kaye et al., 2019; Lozano et al., 2012). Knowledge about host factors contributing to SSTI risk is important to prevent the SSTIs. The genetics of SSTI susceptibility remain largely unknown, and the only previously published genome-wide study on SSTIs is a small family-based linkage study that did not identify significant linkage to any genes for erysipelas or cellulitis susceptibility (Hannula-Jouppi et al., 2013).

A range of cardiometabolic risk factors has been associated with SSTIs (Butler-Laporte et al., 2020; Kaye et al., 2019; Winter-Jensen et al., 2020). Few studies have used genetic variants as instrumental variables (Mendelian randomization [MR]) to assess causality, which may reduce bias owing to reverse causation and confounding (Davies et al., 2018). Increasing body mass index has been found to increase the risk of SSTIs in such a framework (Butler-Laporte et al., 2020; Winter-Jensen et al., 2020), but other cardiometabolic risk factors have, to our knowledge, not been explored.

The aims of this study were to conduct a GWAS on susceptibility to SSTIs, explore possible biological pathways through transcriptome-wide association analyses, and perform MR analyses to investigate the potential causal relationships of cardiometabolic risk factors with SSTIs.

We used two independent cohorts: UK Biobank and Trøndelag Health Study (HUNT), where the UK Biobank served as the discovery cohort in the genome-wide association analyses and the HUNT as the replication cohort. Subjects who had been hospitalized with a primary diagnosis of SSTI served as cases, whereas those who had not been hospitalized with a primary or secondary diagnosis of SSTI were considered controls (Supplementary Material and Methods).

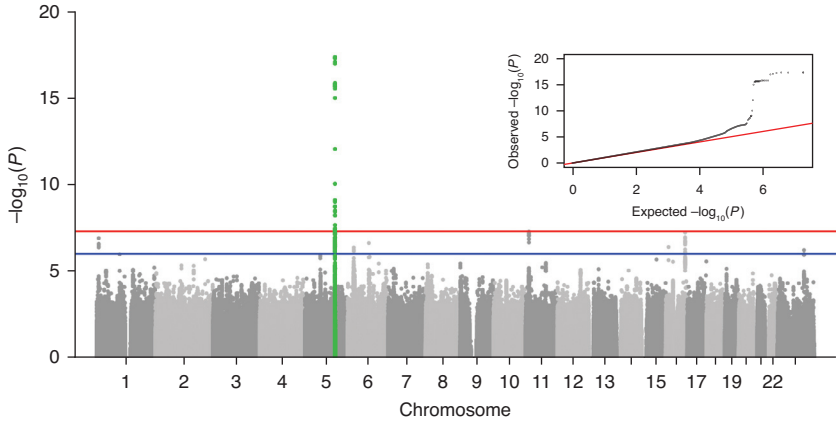

Figure 1. Manhattan plot of results for the meta-analysis. Axes display the $-\log_{10}$ transformed *P*-value by chromosomal position. The blue line indicates genome-wide–suggestive associations ($P < 1e\text{-}6$), and the red line indicates genome-wide–significant associations ($P < 5e\text{-}8$). Genome-wide–significant loci (±500 kb of lead variant) are highlighted in green. The image in the top right corner shows the quantile–quantile plot. Axes display the observed (y-axis) and expected (x-axis) $-\log_{10}$ transformed *P*-value. The black dots represent the observed *P*-values, whereas the red line represents the expected *P*-values under the null distribution. Genomic inflation factor (λ) = 1.01.

Genome-wide association analyses were conducted using scalable and accurate implementation of generalized mixed model, with age, sex, genotype chip, and ancestry-informative principal components as covariates (Zhou et al., 2018), and meta-analyses were conducted using METAL (Supplementary Materials and Methods). Associations with $P < 1e\text{-}6$ and $P < 5e\text{-}8$ were considered genome-wide suggestive and significant, respectively.

We used FUSION to perform transcriptome-wide association analyses by combining the summary statistics from the genome-wide meta-analysis with linkage disequilibrium (European ancestry in 1000 Genomes Project) and reference gene expression panels (Genotype-Tissue Expression, version 7) to estimate the gene expression patterns associated with SSTIs (Gusev et al., 2016). Sun-exposed skin (lower legs) was the tissue of interest for the transcriptome-wide analyses (8,609 genes tested), whereas all the 48 general tissues from Genotype-Tissue Expression, version 7, were analyzed for the chromosome with genome-wide–significant hits (10,518 tests). Bonferroni-corrected threshold for genome-wide significance was $P < 2.6e\text{-}6$.

Two-sample MR analyses were conducted separately for the results from the meta-analysis, UK Biobank, and HUNT. Genetic instruments for body mass index, type-2 diabetes mellitus, low-density lipoprotein cholesterol, systolic blood pressure, lifetime smoking, and sedentary lifestyle were extracted from relevant published

Abbreviations: HUNT, Trøndelag Health Study; MR, Mendelian randomization; SSTI, skin and soft tissue infection

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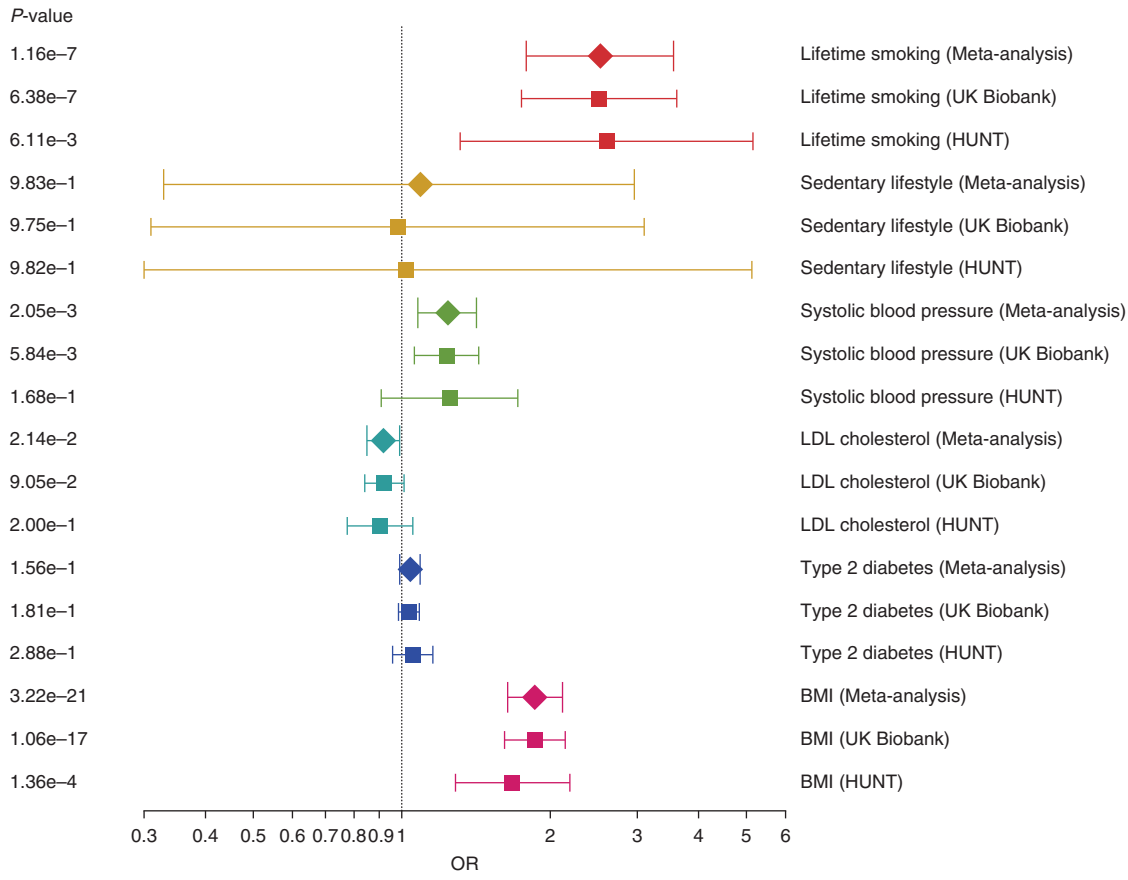

Figure 2. MR analyses of cardiometabolic risk factors on the risk of SSTI. Forest plot of the two-sample inverse-variance weighted MR analyses of cardiometabolic risk factors identified as genetically correlated with SSTI. Each risk factor was evaluated separately using the results from the meta-analysis, UK Biobank, HUNT, and the corresponding risk factors were grouped by color. The x-axis represents the increased OR per SD increase of the genetically predicted risk factor (per unit increase in log OR for genetically proxied type-2 diabetes mellitus liability). BMI, body mass index; HUNT, Trøndelag Health Study; LDL, low-density lipoprotein; MR, Mendelian randomization; SSTI, skin and soft tissue infection.

GWASs (Supplementary Table S1). The TwoSampleMR R package (version 0.5.0) (Hemani et al., 2018) was used to carry out inverse-variance weighted MR analyses (main analyses), along with statistical tests for heterogeneity, simple median, weighted median, and MR Egger (sensitivity analyses).

In both UK Biobank and HUNT, cases at baseline were older, had higher body mass index and systolic blood pressure, were more likely to be male, were more likely to be ever smoker, and were more likely to self-report as diabetic (Supplementary Table S2) than the controls.

The GWAS included 6,107 cases and 399,239 controls from UK Biobank and 1,657 cases and 67,522 controls from HUNT. UK Biobank yielded seven suggestive loci (Supplementary Table S3 and Supplementary Figure S1), of which one was replicated in HUNT: rs3749748 in the *LINC01184/SLC12A2*-gene region on chromosome 5 (Supplementary Figures S2 and S3). In the meta-analysis of 7,764 cases and 466,761 controls, only the locus in *LINC01184/SLC12A2* reached genome-wide significance (Figure 1), whereas two additional loci were close to genome-wide significance: *PSMA1* on chromosome 11 and *GAN* on chromosome 16 (Supplementary Table S3). There was no indication of genomic inflation (Figure 1 and Supplementary Figures S1 and S2).

LINC01184 is part of the long intervening noncoding RNA class of genes that do not encode for proteins but have still been found to modulate inflammation and infection risk (Atianand et al., 2016; Carpenter et al., 2013). *SLC12A2* encodes for the protein NKCC1, which regulates the transportation of chloride, potassium, and sodium across cell membranes, and is key in modulating ion movement across the epithelium, the volume of cells, and antimicrobial activity (Matthay and Su, 2007; Yang et al., 2020).

In the transcriptome-wide association analysis of the skin on the lower legs, the only gene that was statistically significantly associated with SSTIs was *LINC01184* (Supplementary Figure S4). A reduced expression of *LINC01184* was associated with an increased risk of SSTIs. The same association was observed in all tissues but less pronounced in the brain (Supplementary Figure S4).

An increase in genetically predicted body mass index, systolic blood pressure, and smoking increased the risk of SSTIs, whereas increasing low-density lipoprotein cholesterol was associated with a reduced risk of SSTIs (Figure 2). Sensitivity analyses supported the findings from the inverse-variance weighted analyses (Supplementary Table S4).

To our knowledge, this study is a GWAS published on SSTIs, with a large number of cases and controls. We were able to identify a locus—*LINC01184/SLC12A2*—robustly associated with

SSTIs in the discovery cohort and the independent replication cohort. A limitation of our study is that we did not have the power to identify more than one genome-wide–significant locus, which in part may be due to the non-differential misclassification of the outcome, and we thus encourage a replication with meta-analysis in independent cohorts. Of note, whereas the minor allele frequency of rs3749748 in the North-Western European populations is around 23%, it is only 4% in African American populations (Karczewski et al., 2020). It is therefore important to evaluate the populations of different ancestries other than the one currently considered.

In conclusion, we have identified genetic variation in *LINC01184/SLC12A2* to be strongly associated with the risk of SSTIs. Interventions to reduce smoking, hypertension, overweight, and obesity in the population will likely reduce the disease burden of SSTIs.

Data availability statement

Data from the Trøndelag Health Study and UK Biobank are available on application. Gene expression data are available through the FUSION website (http://gusevlab.org/projects/fusion/). Summary statistics are available at the GWAS Catalog (https://www.ebi.ac.uk/gwas) under identification number GCST90013411.

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CONFLICT OF INTEREST

DG is employed part-time by Novo Nordisk, outside of the submitted work. The remaining authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: TR, KVL, ES, JKD, ATD, HMF; Data Curation: TR, HMF, BMB, HR, LFT, CJW, KH, BOÅ; Formal Analysis: TR, HR, LFT; Funding Acquisition: TR, ES, JKD, KH, CJW, BOÅ, JS, ATD, BMB; Investigation: TR, HR, LFT, ES, JKD, KH, CJW, BOÅ, JS, ATD, ML, BMB; Methodology: TR, HR, LFT, DG, SB, ATD, BMB; Project Administration: TR, ES, JKD, BOÅ, KH, CJW, ATD, BMB, ML; Resources: ES, JKD, BOÅ, KH, ATD, JS; Software: DG, SB, BMB, HR, LFT; Supervision: TR, ES, JKD, ATD, BMB, DG, SB, BOÅ, ML, CJW; Validation: HR, LFT, BMB, JS; Visualization: TR, HR, LFT; Writing - Original Draft Preparation: TR; Writing - Review and Editing: TR, KVL, HR, LFT, HMF, JS, ML, DG, SB, CJW, KH, BOÅ, BMB, ATD, ES, JKD

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2021.01.020.

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SUPPLEMENTARY MATERIALS AND METHODS

Material

UK Biobank. Details about the UK Biobank have previously been described (Bycroft et al., 2018). In brief, the cohort consists of 503,325 subjects enrolled between 2006 and 2010 throughout the United Kingdom. Age at baseline was between 38 and 73 years, and 94% of the subjects self-reported being of European ancestry. At baseline, genome-wide genotyping was done on 488,377 individuals, where 84% self-reported that they were of white-British ancestry with European genetic ethnicity. Information on self-reported health and lifestyle was collected, along with measurements such as height and weight. Inpatient hospital data on all the participants were available through electronic record linkage.

Trøndelag Health Study. The Trøndelag Health Study (HUNT) study is a series of surveys conducted in the Nord-Trøndelag region in Norway (~130,000 inhabitants) between 1984 and 2019 on subjects aged ≥20 years (Krokstad et al., 2013). We used data from HUNT2 (1995–1997) and HUNT3 (2006–2008), in which 78,973 subjects representative of the adult Norwegian population participated (Krokstad et al., 2013). Baseline characteristics were collected at study enrollment, and selected measurements were carried out, including height and weight measurement. Information on all hospitalizations in the county and to the regional tertiary care hospital were linked to the study subjects. Through linkage with the Norwegian population registry, we retrieved data on the date of emigration out of the study region and date of death.

Phenotype

Cases and controls were defined similarly to the definitions in the UK Biobank and HUNT. The following International Classification of Diseases (ICD)-9 and ICD-10 codes were considered as skin and soft tissue infection (SSTI) codes: 035 (erysipelas; ICD-9), 729.4 (fasciitis, unspecified; ICD-9), A46 (erysipelas; ICD-10), L03 (cellulitis and acute lymphangitis; ICD-10), and M72.6 (necrotizing fasciitis; ICD-10). These codes are used primarily for bacterial infections, and nonbacterial infections of the skin have other specific codes not considered. Our main definition of SSTI was a case that had been hospitalized with an SSTI as the primary diagnosis. In the sensitivity analysis, we included secondary diagnoses in the definition of SSTI (i.e., SSTIs not the primary cause of hospitalization).

Those who had not been hospitalized with an SSTI (primary or secondary diagnosis) served as controls.

Genotyping

UK biobank. The Affymetrix UK BiLEVE Axiom array was used to genotype the initial 50,000 participants, and the Affymetrix UK Biobank Axiom array was used to genotype the rest of the subjects. Directly genotyped variants were prephased using SHAPEIT3 (O'Connell et al., 2016) and imputed using Impute4 and the UK10K (UK10K Consortium et al., 2015), Haplotype Reference Consortium (UK10K Consortium et al., 2015), and 1000 Genomes Phase 3 (1000 Genomes Project Consortium et al., 2015) reference panels (version 3 of the imputed data). Exclusions were made for variants with imputation score $r^2 < 0.3$. More detail is contained in a previous publication (Bycroft et al., 2018).

HUNT. As previously described, three different Illumina HumanCoreExome arrays were used to genotype the study participants (HumanCoreExome12, version 1.0; HumanCoreExome12, version1.1; and UM HUNT Biobank, version1.0) (Ferreira et al., 2017). Samples with a call rate <99%, with large chromosomal copy number variants, with contamination >2.5% as estimated with BAF Regress (Jun et al., 2012), with genotypic and phenotypic sex discordance, and that were not of European ancestry were excluded, leaving 69,422 genotyped subjects. Genetic variants of Hardy–Weinberg equilibrium ($P < 0.0001$) or with a call rate <99% were excluded. Imputation was done using Minimac3 of 2,201 whole-genome reference sequences from HUNT and Haplotype Reference Consortium, version 1.1, resulting in 24.9 million SNPs ($r^2 > 0.3$). Principal components were calculated using of TRACE (version 1.03), with 938 individuals from the Human Genome Diversity Project serving as reference (Wang et al., 2015, 2014).

Genome-wide association analyses

UK Biobank. Genome-wide association analysis was performed in scalable and accurate implementation of generalized mixed model (version 0.35.8.3) using a linear mixed model that accounts for cryptic relatedness and imbalance in the proportion of cases and controls (Zhou et al., 2018). We included birth year, sex, genotype chip, and the first six ancestry-informative principal components as covariates. We used scalable and accurate implementation of generalized mixed model with the same settings to analyze the X chromosome, coding males as diploid. Variants with minor allele frequency >0.5% were included in the analyses, and dosages were used for imputed variants.

HUNT. Genome-wide association tests were carried using scalable and accurate implementation of generalized mixed model (version 0.29.4) on autosomal chromosomes (Zhou et al., 2018), whereas BOLT-LMM (version 2.3.4) was used in the analysis of the X chromosome, coding males as diploid (Loh et al., 2015). The beta-coefficients from BOLT-LMM were transformed using the formula: log OR = $\beta/(\mu * (1 - \mu))$, where μ = case fraction. The standard errors from BOLT-LMM were transformed using the formula: $SE_{transformed} = SE_{original}/(\mu \times [1 - \mu])$. Age, sex, genotype batch, and the five first ancestry-informative principal components were included as covariates. Variants with minor allele frequency >0.5% were included in the analyses, and dosages were used for imputed variants.

Meta-analysis. We carried out a meta-analysis using METAL (version 2011-03-25), with the use of effect size estimates and standard errors as weights, adjusting for residual population stratification and relatedness through genomic control correction (Willer et al., 2010). A total of 9,211,777 SNPs that were present in both cohorts were included in the meta-analysis.

Ethical approval

The Regional Committee for Medical Research, Health Region IV, Norway approved the HUNT study, and this project is regulated in conjunction with The Norwegian Social Science Data Services. The UK Biobank study has ethical approval from the North West Multi-centre Research Ethics Committee. Approval for individual projects is covered by the Research Tissue Bank.

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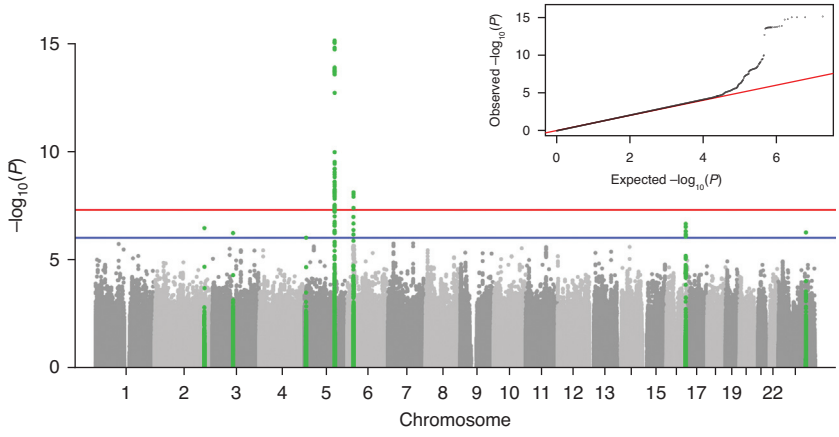
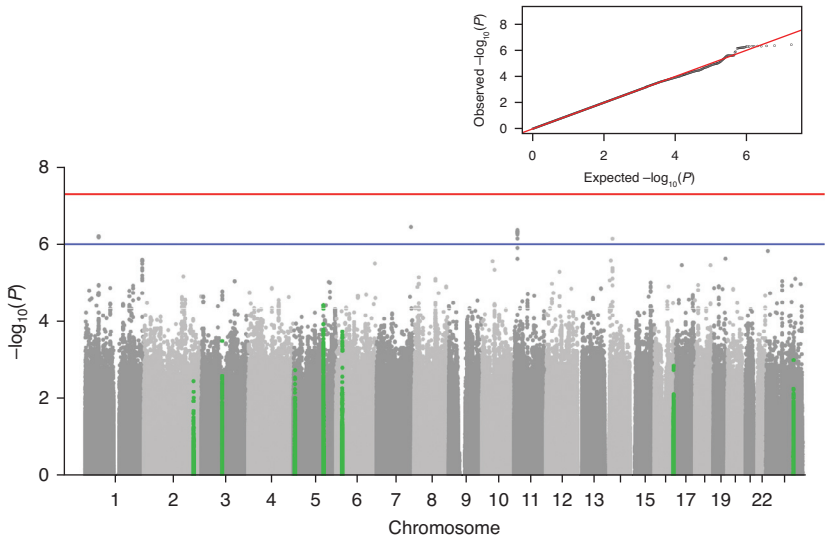
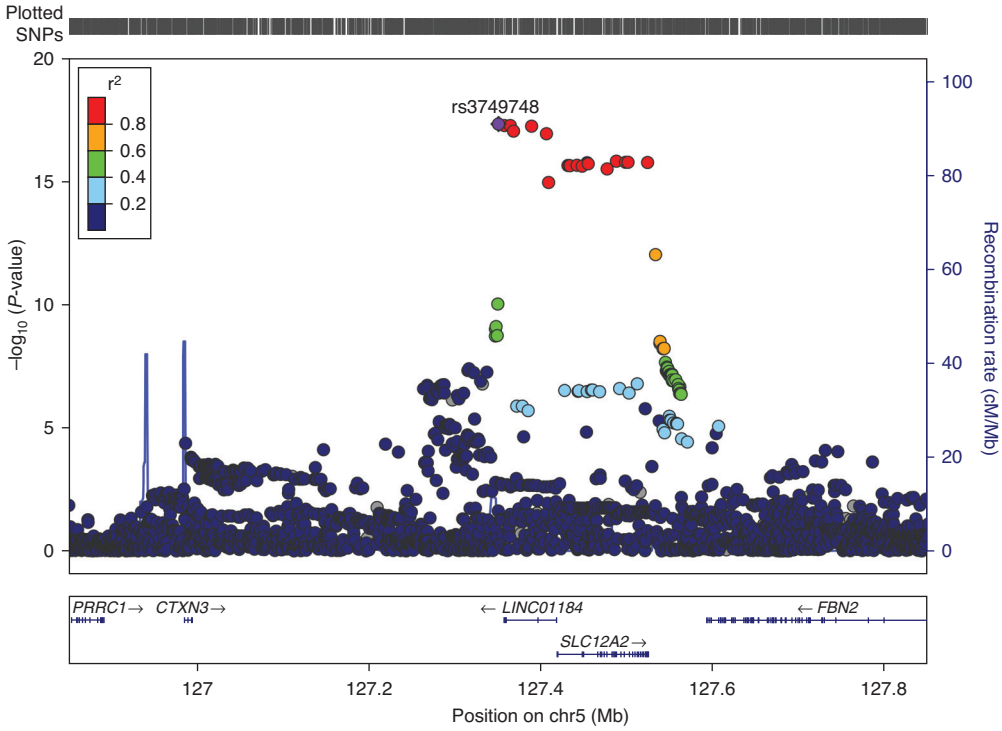


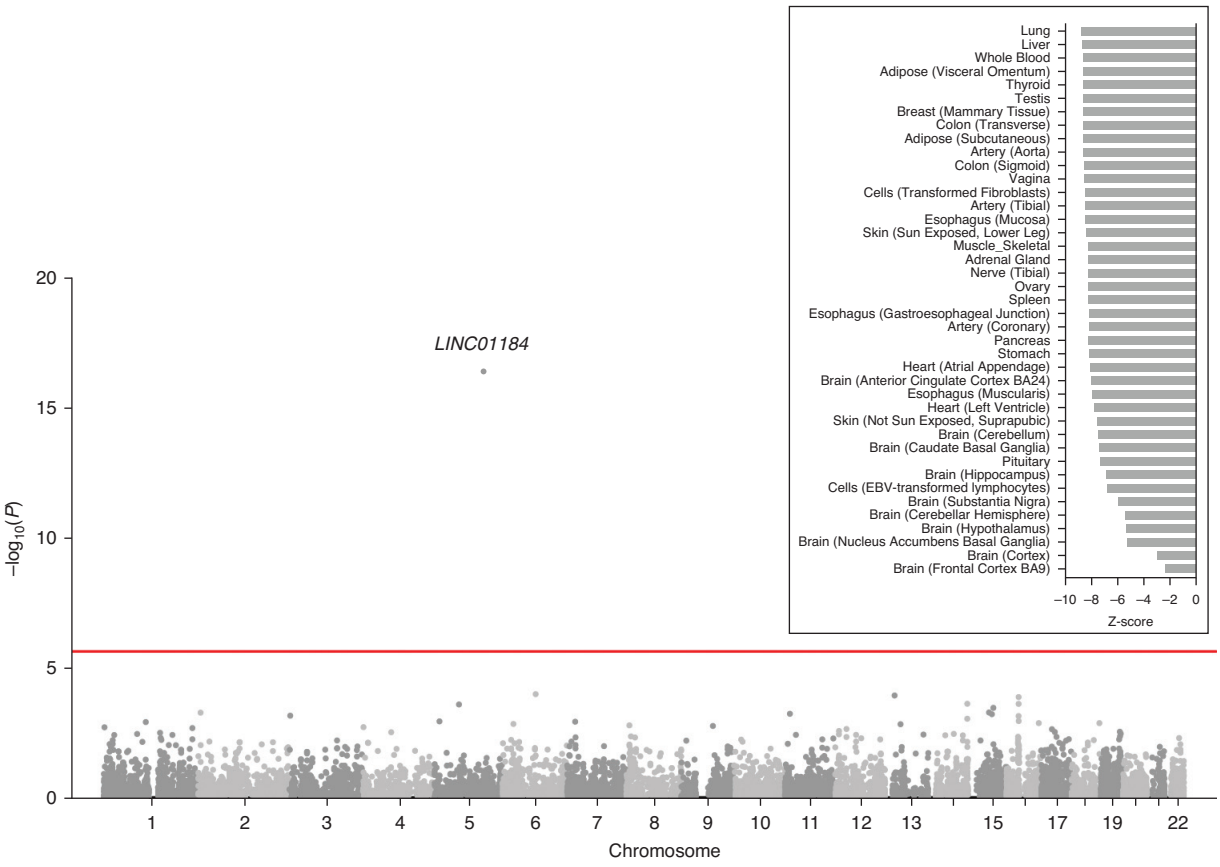
Supplementary Figure S1. Manhattan plot of the results for the discovery stage (UK Biobank). Axes display the $-\log_{10}$ transformed *P*-value by chromosomal position. The blue line indicates the genome-wide–suggestive associations ($P < 1e\text{-}6$), and the red line indicates the genome-wide–significant associations ($P < 5e\text{-}8$). Genome-wide–suggestive loci (±500 kb of lead variant) are highlighted in green. The image in the top right corner shows the quantile–quantile plot. Axes display the observed (y-axis) and expected (x-axis) $-\log_{10}$ transformed *P*-value. The black dots represent the observed *P*-values, whereas the red line represents the expected *P*-values under the null distribution. Genomic inflation factor (λ) = 1.02.kb, kilobase.



Supplementary Figure S2. Manhattan plot of the results for the replication stage (HUNT). Axes display the $-\log_{10}$ transformed *P*-value by chromosomal position. The blue line indicates the genome-wide–suggestive associations ($P < 1e\text{-}6$), and the red line indicates the genome-wide–significant associations ($P < 5e\text{-}8$). Genome-wide–suggestive loci from the discovery stage (±500 kb of lead variant) are highlighted in green. The image in the top right corner shows the quantile–quantile plot. Axes display the observed (y-axis) and expected (x-axis) $-\log_{10}$ transformed *P*-value. The black dots represent the observed *P*-values, whereas the red line represents the expected *P*-values under the null distribution. Genomic inflation factor (λ) = 1.00. HUNT, Trøndelag Health Study; kb, kilobase.



Supplementary Figure S3. Regional plot of the association results of the discovery stage genome-wide–significant locus that was replicated. Associations between genetic variants and SSTI from the meta-analysis are plotted by position (x-axis) and $-\log_{10}$ transformed *P*-values (left y-axis). rs3749748 served as sentinel variant, whereas the remaining variants are color coded in terms of the linkage disequilibrium (r^2) to the sentinel variant. Estimated recombination rates are plotted as light blue lines (right y-axis). The European population from 1000 Genomes Project, November 2014 release, was used as the reference on genome build hg19. chr, chromosome; Mb, megabase; SSTI, skin and soft tissue infection.



Supplementary Figure S4. Manhattan plot of transcriptome-wide association analysis. Each dot represents the association between the predicted gene expressions in the skin on the lower legs with the risk of SSTIs. The red line indicates the statistically significant associations ($P < 2.6e-6$). The image in the top right corner shows the transcriptome association statistic for *LINC01184* in all the 48 tissues from GTEx v7. BA, Brodmann area; EBV, Epstein-Barr virus; GTEx v7, Genotype-Tissue Expression, version 7; SSTI, skin and soft tissue infection.

Supplementary Table S1. Genetic Instruments for Cardiometabolic Exposures

Trait	Sample Size	Population Ancestry	Number of Variants	Variance Explained, %	Reference
Body mass index	681,275	European	595	6.0	(Yengo et al., 2018)
Type-2 diabetes mellitus	74,124 cases and 824,006 controls	European	202	16.3	(Mahajan et al., 2018)
Low-density lipoprotein cholesterol	188,577	European	80	7.9	(Willer et al., 2013)
Systolic blood pressure	318,417	European	192	2.9	(Carter et al., 2019)
Lifetime smoking index	462,690	European	126	0.4	(Wootton et al., 2019)
Sedentary lifestyle	91,105	European	4	0.08	(Doherty et al., 2018)

Only independent SNPs ($r^2 < 0.001$) with $P < 5e-8$ in these GWASs were included.

Supplementary Table S2. Background Characteristics at Entry in the UK Biobank and the HUNT Study

Characteristic	UK Biobank			HUNT		
	Cases (n = 6,107)	Controls (n = 399,239)	All (N = 405,346)	Cases (n = 1,657)	Controls (n = 67,522)	All (N = 69,179)
Female sex	2,535 (41.5)	216,956 (54.3)	219,491 (54.1)	825 (49.8)	35,829 (53.1)	36,654 (53.0)
Age, y	60 (53–65)	58 (51–63)	58 (51–63)	55 (43–68)	46 (34–60)	46 (34–60)
Ever smoker	3,895 (63.8)	240,412 (60.2)	244,307 (60.3)	923 (57.4)	37,518 (56.6)	38,441 (56.6)
Sedentary lifestyle[1]	—	—	(7.1)	192 (13.4)	4,180 (7.0)	4,372 (7.1)
Diabetes (self-reported)	115 (1.9)	2,860 (0.7)	2,975 (0.7)	102 (6.2)	2,003 (3.0)	2,105 (3.1)
Body mass index, kg/m^2	30.6 (6.6)	27.3 (4.7)	27.4 (4.7)	28.8 (5.2)	26.3 (4.1)	26.4 (4.2)
LDL cholesterol, mmol/l	3.4 (0.9)	3.6 (0.9)	3.6 (0.9)	3.8 (1.1)	3.6 (1.1)	3.6 (1.1)
Systolic blood pressure, mmHg	141.1 (19.1)	138.2 (18.6)	138.2 (18.6)	142.1 (22.7)	134.9 (20.9)	135.0 (21.0)

Abbreviation: HUNT, Trøndelag Health Study; LDL, low-density lipoprotein.

Data are presented as mean (SD), median (25th and 75th centile), or number (%).

[1]Sedentary lifestyle: the proportion with sedentary lifestyle among all subjects in UK Biobank was estimated from none of the above from data field 6,164 (types of physical activity in the last 4 weeks) because individual-level data were unavailable; in HUNT, sedentary lifestyle was defined as a self-reported average of 0 hours of low or vigorous physical activity per week in the last year.

Supplementary Table S3. Genetic Variants with $P < 1e\text{-}6$ in the Discovery Cohort or $P < 1e\text{-}7$ in the Meta-Analysis on the Risk of SSTIs

					Discovery (UK Biobank)			Replication (HUNT)			Meta-Analysis	
Variant Name	Chr	Pos (hg19)	Closest Gene	EA/OA	EAF	OR (95% CI)	*P*-Value	EAF	OR (95% CI)	*P*-Value	OR (95% CI)	*P*-Value
rs72989928	2	210,196,618	*MAP2*	G/T	0.017	0.69 (0.60–0.79)	3.5e-7	0.014	0.95 (0.68–1.33)	7.7e-1	0.72 (0.63–0.83)	2.0e-6
rs62267025	3	87,726,132	*AC108749.1*	C/T	0.012	1.60 (1.33–1.92)	6.0e-7	0.010	0.92 (0.63–1.35)	6.6e-1	1.44 (1.22–1.70)	2.0e-5
rs150468829	5	7,081,850	*LINC02196*	A/G	0.009	1.67 (1.36–2.05)	9.7e-7	0.009	0.98 (0.67–1.42)	9.0e-1	1.47 (1.23–1.77)	2.7e-5
rs3749748[1]	5	127,350,549	*LINC01184*	T/C	0.248	1.19 (1.14–1.24)	7.6e-16	0.231	1.15 (1.06–1.25)	6.3e-4	1.18 (1.14–1.23)	4.4e-18
rs115740542	6	26,123,502	*H2BC4*	C/T	0.075	1.23 (1.14–1.31)	7.8e-9	0.091	1.01 (0.90–1.14)	8.4e-1	1.17 (1.10–1.24)	4.2e-7
rs2007361	11	14,662,722	*PSMA1*	G/A	0.342	0.93 (0.90–0.97)	4.0e-4	0.365	0.83 (0.77–0.89)	4.7e-7	0.91 (0.88–0.94)	5.1e-8
rs78625038	16	81,402,279	*GAN*	CT/C	0.006	1.98 (1.53–2.56)	2.2e-7	0.006	1.56 (1.00–2.41)	4.9e-2	1.86 (1.48–2.32)	5.9e-8
rs5910356	X	117,606,177	*WDR44*	T/C	0.058	0.84 (0.79–0.90)	5.6e-7	0.055	1.04 (0.91–1.17)	5.9e-1	0.88 (0.83–0.94)	8.1e-5

Abbreviations: Chr, chromosome; CI, confidence interval; EA, effect allele; EAF, effect allele frequency; HUNT, Trøndelag Health Study; OA, other allele; Pos, chromosome position.
[1]Suggestive variants ($P < 1e\text{-}6$) in the discovery cohort that replicate in the HUNT cohort ($P < 7.1e\text{-}3$ and β coefficient in the same direction) are presented.

Supplementary Table S4. MR Sensitivity Analyses of Cardiometabolic Risk Factors on the Risk of SSTI

Trait	UK Biobank			HUNT			Meta-Analysis		
	OR (95% CI) or Q	*P*-Value	Number of SNPs	OR (95% CI) or Q	*P*-Value	Number of SNPs	OR (95% CI) or Q	*P*-Value	Number of SNPs
Lifetime smoking									
IVW	2.51 (1.75–3.61)	6.38e-7	126	2.61 (1.31–5.17)	6.11e-3	125	2.53 (1.79–3.56)	1.16e-7	125
Heterogeneity IVW	135.53	2.45e-1	126	125.35	4.49e-1	125	148.49	6.62e-2	125
Simple median	2.45 (1.46–4.12)	7.31e-4	126	2.92 (1.03–8.28)	4.44e-2	125	2.67 (1.67–4.28)	4.03e-5	125
Weighted median	2.36 (1.38–4.03)	1.69e-3	126	3.16 (1.18–8.42)	2.17e-2	125	2.17 (1.34–3.52)	1.71e-3	125
MR Egger	1.52 (0.36–6.44)	5.71e-1	126	7.17 (0.45–113.72)	1.65e-1	125	2.06 (0.52–8.06)	3.04e-1	125
MR Egger intercept	1.01 (0.99–1.02)	4.81e-1	126	0.99 (0.97–1.02)	4.60e-1	125	1.00 (0.99–1.02)	7.61e-1	125
Sedentary lifestyle									
IVW	0.98 (0.31–3.11)	9.75e-1	4	1.02 (0.20–5.13)	9.82e-1	4	1.09 (0.33–2.96)	9.83e-1	4
Heterogeneity IVW	9.30	2.55e-2	4	4.89	1.80e-1	4			4
Simple median	0.67 (0.29–1.52)	3.34e-1	4	1.00 (0.21–4.81)	9.99e-1	4	0.86 (0.41–1.80)	6.93e-1	4
Weighted median	0.65 (0.27–1.54)	3.29e-1	4	1.01 (0.22–4.66)	9.89e-1	4	0.85 (0.41–1.78)	6.72e-1	4
MR Egger	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
MR Egger intercept	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Systolic blood pressure									
IVW	1.23 (1.06–1.43)	5.84e-3	192	1.25 (0.91–1.72)	1.68e-1	187	1.24 (1.08–1.42)	2.05e-3	187
Heterogeneity IVW	182.96	6.49e-1	192	217.98	5.42e-2	187	185.37	4.99e-1	187
Simple median	1.43 (1.14–1.79)	1.70e-3	192	1.14 (0.74–1.76)	5.61e-1	187	1.21 (1.00–1.47)	4.78e-2	187
Weighted median	1.27 (1.01–1.60)	3.82e-2	192	1.31 (0.82–2.09)	2.60e-1	187	1.10 (0.90–1.35)	3.34e-1	187
MR Egger	0.76 (0.47–1.21)	2.45e-1	192	2.52 (0.93–6.87)	7.19e-2	187	0.99 (0.65–1.52)	9.77e-1	187
MR Egger intercept	1.01 (1.00–1.02)	3.23e-2	192	0.99 (0.97–1.01)	1.50e-1	187	1.00 (1.00–1.01)	2.87e-1	187
Low-density lipoprotein cholesterol									
IVW	0.92 (0.84–1.01)	9.05e-2	80	0.90 (0.78–1.05)	2.00e-1	78	0.92 (0.85–0.99)	2.14e-2	78
Heterogeneity IVW	112.71	7.65e-3	80	48.79	9.95e-1	78	83.58	2.85e-1	78
Simple median	0.89 (0.77–1.03)	1.17e-1	80	0.99 (0.77–1.28)	9.46e-1	78	0.87 (0.77–0.99)	3.05e-2	78
Weighted median	0.90 (0.79–1.01)	7.64e-2	80	0.98 (0.78–1.25)	8.95e-1	78	0.91 (0.82–1.01)	8.14e-2	78
MR Egger	0.89 (0.78–1.02)	1.01e-1	80	0.89 (0.71–1.12)	3.13e-1	78	0.89 (0.80–0.99)	3.81e.2	78
MR Egger intercept	1.00 (0.99–1.01)	4.88e-1	80	1.00 (0.99–1.02)	8.38e-1	78	1.00 (1.00–1.01)	4.58e-1	78
Type-2 diabetes mellitus									
IVW	1.03 (0.98–1.09)	1.81e-1	199	1.05 (0.96–1.16)	2.88e-1	195	1.04 (0.99–1.09)	1.56e-1	195
Heterogeneity IVW	243.51	1.93e-2	199	216.12	1.32e-1	195	263.37	6.75e-4	195
Simple median	1.05 (0.97–1.14)	1.99e-1	199	1.07 (0.92–1.23)	3.85e-1	195	1.09 (1.02–1.17)	1.47e-2	195
Weighted median	0.96 (0.89–1.04)	3.43e-1	199	0.97 (0.81–1.16)	7.39e-1	195	0.97 (0.90–1.04)	3.35e-1	195
MR Egger	0.90 (0.81–1.00)	4.85e-2	199	1.05 (0.85–1.29)	6.54e-1	195	0.92 (0.83–1.02)	1.26e-1	195
MR Egger intercept	1.01 (1.00–1.02)	3.61e-3	199	1.00 (0.99–1.01)	9.64e-1	195	1.01 (1.00–1.02)	1.38e-2	195

(*continued*)

Supplementary Table S4. Continued

Trait	UK Biobank			HUNT			Meta-Analysis		
	OR (95% CI) or Q	*P*-Value	Number of SNPs	OR (95% CI) or Q	*P*-Value	Number of SNPs	OR (95% CI) or Q	*P*-Value	Number of SNPs
Body mass index									
IVW	1.86 (1.62−2.15)	1.06e-17	594	1.68 (1.29−2.19)	1.36e-4	580	1.86 (1.64−2.12)	3.22e-21	580
Heterogeneity IVW	658.06	3.26e-2	594	532.31	9.18e-1	580	641.16	3.72e-2	580
Simple median	1.91 (1.56−2.34)	6.17e-10	594	1.62 (1.11−2.37)	1.28e-2	580	1.92 (1.60−2.31)	2.29e-12	580
Weighted median	1.63 (1.33−2.00)	2.06e-6	594	1.53 (1.02−2.30)	4.03e-2	580	1.83 (1.51−2.21)	7.05e-10	580
MR Egger	1.70 (0.95−3.04)	7.38e-2	594	1.02 (0.34−3.05)	9.78e-1	580	1.41 (0.83−2.41)	2.03e-1	580
MR Egger intercept	1.00 (0.99−1.01)	7.50e-1	594	1.01 (0.99−1.02)	3.55e-1	580	1.00 (1.00−1.01)	2.96e-1	580

Abbreviations: CI, confidence interval; HUNT, Trøndelag Health Study; IVW, inverse-variance weighted; MR, Mendelian randomization; N/A, not applicable; SSTI, SSTI, skin and soft tissue infection.
The effect estimates are presented as OR per SD increase of the genetically predicted risk factor (per unit increase in log OR for genetically proxied type-2 diabetes mellitus liability). For the heterogeneity test of the IVW analysis, the Q-statistic along with its *P*-value is presented.