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The relationship between duration of psoriasis, vascular inflammation and cardiovascular events

Alexander Egeberg, MD, PhD[1], **Lone Skov, MD, PhD, DMSc**[1], **Aditya A. Joshi, MD**[2], **Lotus Mallbris, MD, PhD**[3], **Gunnar H. Gislason, MD, PhD**[4,5,6], **Jashin J. Wu, MD**[7], **Justin Rodante, PA-C**[2], **Joseph B. Lerman, BA**[2], **Mark A. Ahlman, MD**[2], **Joel M. Gelfand, MD, MSCE**[8], and **Nehal N. Mehta, MD**[2]

[1]Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark

[2]National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda MD, USA

[3]Unit of Dermatology and Venerology, Karolinska Institutet, Stockholm, Sweden

[4]Department of Cardiology, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark

Corresponding author: Alexander Egeberg, Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark, Telephone: (0045) 24215421, alexander.egeberg@gmail.com OR Nehal Mehta, Section of Inflammation and Cardiometabolic Diseases, National Heart, Lung and Blood Institute, Bethesda, MD, USA, Telephone: 1-301-827-0483, nehal.mehta@nih.gov.

Study/ethical approval

Study approval was obtained from by the Danish Data Protection Agency (ref. 2007-58-0015, int. ref. GEH-2014-018, I-Suite 02736). Review of an ethics committee is not required for register studies in Denmark. Data for the cohort study at the National Heart, Lung, and Blood Institute were obtained under the protocol titled “Psoriasis, Atherosclerosis and Cardiometabolic Disease Initiative (PACI)” (NCT01778569).

Author Contributions:

Dr. Egeberg (Danish cohort) and Dr. Mehta (NIH cohort) had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Egeberg, Skov, Mallbris, Gislason, Gelfand, and Mehta. *Acquisition, analysis, and interpretation of data:* (NIH cohort): Joshi, Ahlman, Rodante, Lerman, Gelfand, and Mehta (Danish cohort): Egeberg and Gislason. *Drafting of the manuscript:* Egeberg and Mehta. *Critical revision of the manuscript for important intellectual content:* All authors. *Statistical analysis:* Egeberg, Gislason and Joshi. *Obtained funding:* Mehta. *Administrative, technical, or material support:* Egeberg, Skov, Gislason and Mehta. *Study supervision:* Egeberg and Mehta.

Disclosures/Conflicts of interest

Dr. Egeberg has received research funding from Pfizer and Eli Lilly, and honoraria as consultant and/or speaker from Pfizer, Eli Lilly, Novartis, Galderma, and Janssen Pharmaceuticals. Dr. Skov has been a paid speaker for Pfizer, AbbVie, Eli Lilly, Novartis and LEO Pharma, and has been a consultant or served on Advisory Boards with Pfizer, AbbVie, Janssen Cilag, Novartis, Eli Lilly, LEO Pharma and Sanofi. She has served as an investigator for Pfizer, AbbVie, Eli Lilly, Novartis, Amgen, Regeneron and LEO Pharma and received research and educational grants from Pfizer, AbbVie, Novartis, Sanofi, Janssen Cilag and Leo Pharma. Dr. Mallbris is currently employed by Eli Lilly. Dr. Gislason is supported by an unrestricted research scholarship from the Novo Nordisk Foundation and reports research grants from Pfizer, Bristol-Myers Squibb, AstraZeneca, Bayer and Boehringer Ingelheim. Dr. Wu received research funding from AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Coherus Biosciences, Dermira, Eli Lilly, Janssen, Merck, Novartis, Pfizer, Regeneron, Sandoz, and Sun Pharmaceutical Industries; he is a consultant for AbbVie, Amgen, Celgene, Dermira, Eli Lilly, Pfizer, Regeneron, and Sun Pharmaceutical Industries. In the previous 12 months Dr. Gelfand served as a consultant for Coherus (DSMB), Dermira, Janssen Biologics, Merck (DSMB), Novartis Corp, Regeneron, Sanofi and Pfizer Inc., receiving honoraria; and receives research grants (to the Trustees of the University of Pennsylvania) from Abbvie, Janssen, Novartis Corp, Regeneron, Sanofi, Celgene, and Pfizer Inc.; and received payment for continuing medical education work related to psoriasis that was supported indirectly by Lilly and Abbvie. Dr. Gelfand is a co-patent holder of resiquimod for treatment of cutaneous T cell lymphoma. Dr. Mehta is a full-time United States government employee.

[5]The Danish Heart Foundation, Copenhagen, Denmark

[6]The National Institute of Public Health, University of Southern Denmark, Copenhagen

[7]Kaiser Permanente Los Angeles Medical Center, Los Angeles, California, United States

[8]Department of Dermatology, Department of Biostatistics and Epidemiology, and Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia PA, USA

Abstract

Background—Psoriasis is associated with risk of cardiovascular (CV) disease (CVD) and major adverse CV events (MACE). Whether psoriasis duration affects risk of vascular inflammation and MACE has not been well characterized.

Objectives—We utilized two resources to understand the effect of psoriasis duration on vascular disease and CV event: 1) a human imaging study and; 2) a population-based study of CVD events.

Methods—1) Patients with psoriasis (n=190) underwent ^{18}F-fluorodeoxyglucose positron emission tomography (18-FDG PET) computed tomography (CT) (duration effect reported as a β-coefficient). 2) MACE risk was examined using nationwide registries (adjusted hazard ratios [HRs]) in patients with psoriasis (n=87,161) versus the general population (n=4,234,793).

Results—In the human imaging study, patients were young, of low CV risk by traditional risk scores and had a high prevalence of cardiometabolic diseases. Vascular inflammation by 18-FDG PET/CT was significantly associated with disease duration (β=0.171, p=0.002). In the population-based study, psoriasis duration had strong relationship with MACE (1.0% per additional year of psoriasis duration (HR 1.010; 95% confidence interval 1.007–1.013).

Limitations—These studies utilized observational data.

Conclusion—We found detrimental effects of psoriasis duration on vascular inflammation and MACE, suggesting that cumulative duration of exposure to low-grade chronic inflammation may accelerate vascular disease development and MACE. Providers should consider inquiring about duration of disease to counsel for heightened CVD risk in psoriasis.

Keywords

Psoriasis; Inflammation; Cardiovascular disease; 18-FDG PET/CT

Introduction

Patients with psoriasis have an increased incidence and prevalence of cardiovascular (CV) risk factors[1] and CV disease (CVD).[2–5] Vascular inflammation by ^{18}F-fluorodeoxyglucose positron emission tomography computed tomography (18-FDG PET/CT), which is prognostic for future CV events, is increased in patients with psoriasis.[6–8] Cumulative exposure to inflammation is linked to increased atherosclerosis and CV events, suggesting that longer disease duration might increase the risk for CVD and CV events. Thus, disease duration may represent a potentially easily obtainable measure of risk for CVD in inflammatory-based diseases.

We investigated whether longer duration of psoriasis would increase vascular inflammation and major adverse cardiovascular event (MACE) due to the longer exposure to chronic, low-grade systemic inflammation observed in psoriasis.

Materials

Detailed descriptions of study approvals, data sources, and methods are available online.[9]

Data sources

Data for the cohort study at the National Heart, Lung, and Blood Institute were obtained under the protocol titled "Psoriasis, Atherosclerosis and Cardiometabolic Disease Initiative (PACI)" (NCT01778569). Complete and accurate data (including medical conditions, pharmacotherapy, treatment interventions and surgical procedures, income, and vital statistics) on the Danish population are available from nationwide registers, which can be linked at individual-level.

Study populations

National Institute of Health (NIH) cohort—The longitudinal cohort study group ("NIH cohort") comprised 190 consecutive patients with psoriasis, recruited from January 2013 through June 2016. A dermatologist or a certified physician confirmed the onset and duration of psoriasis, and assessed psoriasis severity using the PASI and body surface area (BSA) scores. Clinical parameters including blood pressure, height, weight, waist and hip circumferences were measured. Laboratory parameters including fasting blood glucose, fasting lipid panel, white blood count with differential, and systemic inflammatory markers including Hs-CRP and erythrocyte sedimentation rate (ESR) were evaluated in a clinical laboratory. All patients underwent 18-FDG PET/CT scans for quantification of vascular inflammation[6–8].

Total Danish population cohort—The total Danish population cohort (henceforth "population cohort") comprised all Danish citizens ≥18 years, alive and resident in Denmark on 1 January 2008 (study start).

Outcomes

NIH cohort—The primary outcome in the NIH cohort was TBR assessed by 18-FDG PET/CT (Siemens Biograph mCT PET/CT 64-slice scanner). 18-FDG uptake within the aorta was measured by utilizing dedicated analysis software for PET/CT (Extended Brilliance™ Workspace, Phillips Healthcare, Andover, MA, USA). One value of TBR was used as the primary outcome for each patient. The association between vascular inflammation and MACE was not examined. Detailed description of TBR calculation is provided in our previous work[10].

Population cohort—The primary outcome in the population cohort was the first occurrence of a MACE, i.e. a composite of MI, ischemic stroke, and CV death, respectively. Secondary outcomes included specific occurrences of MI, ischemic stroke, and CV death.

Covariates

NIH Cohort—Baseline treatment for NIH cohort was defined for any of the following therapies: systemic non-biologic agents (henceforth “systemic”) or biologic therapy (systemic steroids, methotrexate, adalimumab, etanercept, and ustekinumab), statins, psoralen plus ultraviolet A (PUVA) or ultraviolet B (UVB), and topical treatments. Patients completed survey-based questionnaires regarding smoking, previous CVD, family history of CVD, and previous established diagnoses of hypertension and diabetes. Patient responses were then ascertained by interview with the physician. All parameters were assessed up to 12 months prior to study inclusion.

Population cohort—Baseline treatment up to 6 months before study inclusion was defined for the following therapies: biologics (adalimumab, efalizumab, etanercept, infliximab, and ustekinumab), cholesterol-lowering drugs, cyclosporine, methotrexate, PUVA/UVB, retinoids (acitretin/etretinate), and topical vitamin D analogues. Baseline comorbidity was assessed up to 5 years prior to study inclusion for the following conditions: alcohol abuse, smoking, CVD, diabetes, hypertension, and psoriatic arthritis. We calculated age-standardized socioeconomic status based on the average gross annual income during a 5-year period before study inclusion.

Statistical analysis

Summary statistics were presented as means with SD for normally distributed variables, medians and IQR for non-normally distributed continuous variables and frequencies for categorical variables. Normality was assessed by skewness and kurtosis. Parametric variables were compared between groups using Student’s t-test while Mann-Whitney U test was performed for non-parametric variables. Dichotomous variable comparisons were done using Pearson’s chi-square test.

NIH Cohort—Unadjusted regression analyses were performed to evaluate for potential relationships between cardiometabolic variables and psoriasis duration. We conducted multivariable linear regression analyses to evaluate the associations of vascular inflammation (TBR) with psoriasis duration. These analyses were adjusted for age at onset of psoriasis, sex, and traditional CV risk assessed by Framingham Risk Score, history of CVD, diabetes, hypertension, treatment with statins, smoking, and alcohol abuse. We assessed the ‘F’ statistics along with p-values as well as the root mean squared error values to assess for the goodness of fit for every model.

Population cohort—Incidence rates were summarized per 1,000 person-years, and Cox regression was performed to estimate hazard ratios (HRs). Multivariable models was adjusted for age, sex, socioeconomic status, previous CVD, smoking, alcohol abuse, diabetes, hypertension, and use of statins. We performed separate sensitivity analyses, where patients with psoriatic arthritis, and those with previous CVD, respectively, were excluded. We performed additional analyses where psoriasis was defined only using hospital diagnoses. Moreover, we did analyses where the population cohort was divided into older (born prior to 1960) and younger (born in or after 1960) individuals, respectively. Lastly, we repeated our analyses with adjustment for age at onset of psoriasis.

Results were presented with 95% confidence intervals (CIs) where applicable, and p-values less than 0.05 were considered statistically significant. Statistical analyses were performed with the STATA versions 12.0 and 13.0 (StataCorp, College Station, TX, USA) and SAS version 9.4 (SAS Institute Inc. Cary, NC, USA).

Results

National Institute of Health (NIH) cohort

The NIH cohort comprised 190 patients with mild-to-moderate psoriasis (Supplementary Table 1), primarily middle aged men (57% men), overweight, with mild insulin resistance (median insulin resistance of 2.77) but at low CV risk by Framingham risk score. Vascular inflammation assessed by target-to-background ratio (TBR) (mean ± standard deviation [SD] 1.70±0.26) demonstrated increased vascular inflammation.[11] Strong associations with vascular inflammation were seen for male sex, smoking, Framingham 10-year risk, and BMI. The per-year incremental effect of psoriasis duration on vascular inflammation (assessed by TBR) showed that duration of psoriasis was associated with increased vascular inflammation (β=0.086, p=0.040), a relationship that persisted beyond adjustment for traditional cardiovascular risk factors (β=0.171, p=0.002) (Figure 1 and Supplementary Table 2).

Population cohort

The population cohort comprised a total of 4,321,954 individuals, including 87,161 patients with psoriasis (maximum disease duration was 31.1 years) (Table 1). During a mean (SD) follow-up of 4.7 (0.9) years, a total of 152,122 and 4,472 patients experienced a MACE, in the general population (incidence rate/1,000 person-years: 7.56; 95% CI 7.52–7.60), and in patients with psoriasis (incidence rate/1,000 person-years: 10.94; 95% CI 10.62–11.26), respectively.

In unadjusted analyses, psoriasis was associated with 3.9% increased risk of MACE per additional year of disease duration, and in multivariable analysis, the risk of MACE increased with 1.0% per additional year of psoriasis duration (HR 1.010; 95% CI 1.007–1.013) (Table 2 and Figure 2). For secondary endpoints, the multivariable HRs associated with duration of psoriasis were 1.006 (95% CI 1.001–1.012) for myocardial infarction (MI), 1.011 (95% CI 1.007–1.016) for ischemic stroke, and 1.011 (95% CI 1.007–1.015) for CV death, respectively.

Discussion

We utilized a human imaging study and a population-based study to investigate whether the duration of psoriasis increases the risk of CVD and MACE, and present novel and convincing evidence to suggest a detrimental effect of psoriasis duration on CVD beyond traditional CV risk factors, even in patients with low CV risk scores. Notably, every 1 SD increase in duration of psoriasis increases the TBR by 2.5%, which roughly translates into an absolute increase of 10% in future adverse events based on a recent large population study.[12]

Similar to rheumatoid arthritis,[13] most but not all studies have associated psoriasis with an increased risk of CVD,[2–5, 14–16] yet data suggest that classical CV risk factors alone do not fully capture this heightened risk, and systemic inflammation has been put forward as a potential explanation for the link between psoriasis and CVD. Along this line, inflammation is associated with impaired insulin sensitivity, carotid intima-media thickening, endothelial dysfunction, aortic stiffness, vascular inflammation, and coronary plaque burden and such CVD markers occur more frequently in patients with psoriasis.[17–19] These insults could occur due to a consistent vascular damage consequent to immune activation in those with longer duration of disease.

We opted for a translational epidemiological approach, utilizing a human imaging study combined with observational registry data to emphasize the putative clinical relevance of increased vascular inflammation observed in our study. Specifically, we found a 1% increase in future CV event risk per additional year of disease duration, an effect size similar to smoking. Each of components of the composite outcome of MACE were also increased with longer duration of disease suggesting that duration of inflammation increases all vascular disease related events. Nevertheless, we emphasize that the independent association between psoriasis and CVD remains a topic of ongoing debate,[20] as does the effect of systemic therapy on the vascular inflammation and CV events.[21]

A limitation in the population cohort was a lack of information for body mass index and levels of physical exercise. However, such data were available in the NIH cohort, and adjustment for body mass index did not significantly change the relationship between duration of disease and vascular inflammation. Furthermore, previous CVD and diabetes, two major predictors of MACE in the population cohort did not relate to vascular inflammation in the NIH cohort. This is likely due to the low number of patients with these characteristics in the NIH cohort. Important strengths include the sheer number of participants and the high accuracy of the nationwide registries, which minimized bias due to sex, age, concurrent medication, and socioeconomic status. Observational data alone from a single study is not sufficient to establish causality. However, comparable findings across different populations, using our approach of both observational and vascular imaging data add strength and credibility to our findings and the results are consistent with prior work demonstrating that duration of psoriasis is an independent risk factor for MI and coronary artery disease measured by angiography.[22, 23]

In conclusion, we have provided strong novel evidence that duration of psoriasis increases vascular inflammation and the risk of MACE. Providers should consider inquiring about duration of psoriasis when assessing CV risk stratification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Design and conduct of the study	Yes__	No _X_
Collection, management, analysis and interpretation of data	Yes__	No _X_
Preparation, review, or approval of the manuscript	Yes__	No _X_
Decision to submit the manuscript for publication	Yes__	No _X_

Abbreviations

18-FDG PET	^{18}F-fluorodeoxyglucose positron emission tomography
CCTA	Coronary computed tomography angiography
CT	Computed tomography
CV	Cardiovascular
CVD	Cardiovascular disease
CI	Confidence interval
HR	Hazard ratio
IQR	Interquartile range
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
NIH	National Institute of Health
PUVA	Psoralen plus ultraviolet A
SD	Standard deviation
TBR	Target-to-background ratio
UVB	Ultraviolet B

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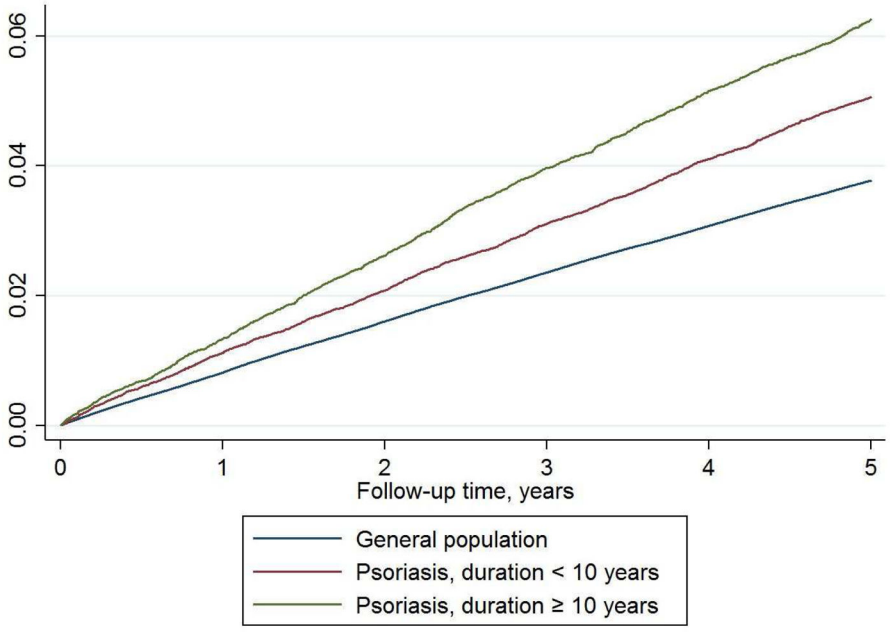

Figure 1. Nelson-Aalen cumulative hazards graph of the population cohort

MACE risk in patients with psoriasis stratified based on disease duration less (n=57,941) or more (n=29,220) than 10 years, compared with the general population (n=4,234,793)

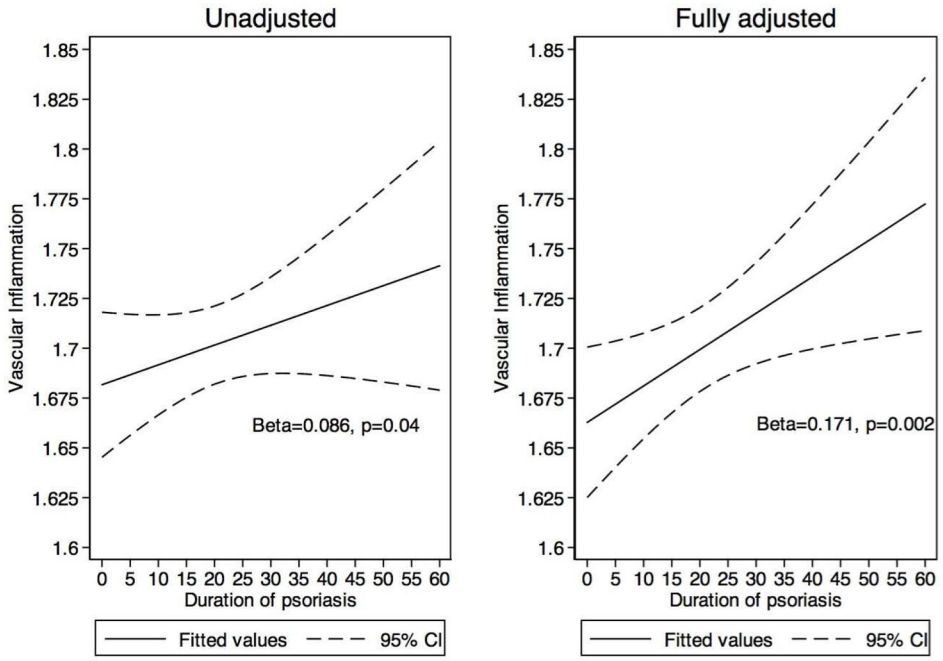

Figure 2. Association between vascular inflammation and psoriasis disease duration in the NIH cohort

Unadjusted and fully adjusted regression plots demonstrate a direct association between psoriasis disease duration and vascular inflammation in the NIH cohort beyond traditional cardiovascular risk factors.

Table 1

Baseline characteristics of the total population cohort

	Reference population (n=4,234,793)	Psoriasis (n=87,161)
Age, mean (SD)	48.6 (18.0)	53.8 (16.3)
Sex, n (%)		
Women	2,148,653 (50.7)	45,809 (52.6)
Men	2,086,140 (49.3)	41,352 (47.4)
Duration of psoriasis		
Mean (SD)	NA	7.8 (5.2)
Median (IQR)	NA	7.7 (3.9–11.2)
Age at onset of psoriasis, mean (SD)	NA	46.0 (16.6)
Socioeconomic status, mean (SD)	2.0 (1.3)	2.2 (1.3)
Hospitalized (inpatient) for psoriasis, n (%)	NA	4,975 (5.7)
Smoking, n (%)	337,551 (8.0)	10,459 (12.0)
Comorbidity, n (%)		
Alcohol abuse	58,671 (1.4)	1,672 (1.9)
Cardiovascular disease	364,023 (8.6)	11,737 (13.5)
Diabetes	151,043 (3.6)	5,376 (6.2)
Hypertension	506,836 (12.0)	15,908 (18.3)
Psoriatic arthritis	2,515 (0.1)	5,742 (6.6)
Treatment *, n (%)		
Biologics	2,760 (0.1)	663 (0.8)
Cholesterol lowering drugs	384,425 (9.1)	12,436 (14.3)
Cyclosporine	985 (0.0)	193 (0.2)
Methotrexate	13,971 (0.3)	3,189 (3.7)
PUVA/UVB phototherapy	346 (0.0)	264 (0.3)
Retinoids (acitretin/etretinate)	395 (0.0)	553 (0.6)
Topical vitamin D analogues	NA	12,621 (14.5)

IQR, interquartile range; NA, not applicable; PUVA, psoralen plus ultraviolet A; SD, standard deviation; UVB, ultraviolet B

*Within the last 6 months

Table 2

Univariable and multivariable hazard ratios of MACE in patients with psoriasis compared with the general population

	Univariable			Multivariable		
	Hazard ratio	**95% CI**	**p-value**	**Hazard ratio**	**95% CI**	**p-value**
Duration of psoriasis	**1.039**	**1.036–1.042**	**<0.0001**	**1.010**	**1.007–1.013**	**<0.0001**
Age	1.087	1.087–1.087	<0.0001	1.075	1.075–1.076	<0.0001
Male sex	1.230	1.218–1.242	<0.0001	1.516	1.501–1.532	<0.0001
Socio-economic status						
0 (lowest)	1.722	1.695–1.748	<0.0001	1.118	1.101–1.136	<0.0001
1 (below average)	2.355	2.321–2.389	<0.0001	1.113	1.096–1.130	<0.0001
2 (average)		(reference)			(reference)	
3 (above average)	0.536	0.526–0.547	<0.0001	0.855	0.838–0.873	<0.0001
4 (highest)	0.478	0.468–0.488	<0.0001	0.744	0.729–0.760	<0.0001
Previous CVD	8.667	8.581–8.755	<0.0001	2.278	2.252–2.305	<0.0001
Statin use	3.594	3.556–3.631	<0.0001	0.908	0.897–0.919	<0.0001
Diabetes	3.743	3.692–3.795	<0.0001	1.420	1.399–1.441	<0.0001
Hypertension	5.721	5.665–5.778	<0.0001	1.394	1.379–1.411	<0.0001
Alcohol abuse	1.612	1.565–1.659	<0.0001	1.905	1.850–1.961	<0.0001
Smoking	2.654	2.620–2.689	<0.0001	1.697	1.676–1.720	<0.0001

CVD, cardiovascular disease; CI, confidence interval