Regional and temporal differences in the associations between cardiovascular disease and its classic risk factors: An analysis of 49 cohorts from 11 European countries

Reinikainen, J., Kuulasmaa, K., Oskarsson, V., Amouyel, P., Biasch, K., Brenner, H., De Ponti, R., Donfrancesco, C., Drygas, W., Ferrieres, J., Grassi, G., Grimsgaard, S., Iacoviello, L., Jousilahti, P., Kårhus, L. L., Kee, F., Linneberg, A., Luksiene, D., Mariño, J., ... Niiranen, T. (2023). Regional and temporal differences in the associations between cardiovascular disease and its classic risk factors: An analysis of 49 cohorts from 11 European countries. *European Journal of Preventive Cardiology*. Advance online publication. https://doi.org/10.1093/eurjpc/zwad359

Published in:
European Journal of Preventive Cardiology

Document Version:
Peer reviewed version

Regional and temporal differences in the associations between cardiovascular disease and its classic risk factors

An analysis of 49 cohorts from 11 European countries

Short running head: Associations between CVD and its risk factors

Jaakko Reinikainen[1], Kari Kuulasmaa[1], Viktor Oskarsson[2], Philippe Amouyel[3], Katia Biasch[4], Hermann Brenner[5, 6], Roberto De Ponti[7], Chiara Donfrancesco[8], Wojciech Drygas[9, 10], Jean Ferrieres[11], Guido Grassi[12], Sameline Grimsgaard[13], Licia Iacoviello[14, 15], Pekka Jousilahti[1], Line L. Kårhus[16], Frank Kee[17], Allan Linneberg[16, 18], Dalia Luksiene[19], Joany Mariño[20], Marie Moitry[4], Luigi Palmieri[8], Annette Peters[21, 22, 23], Aleksandra Piwonska[9], Fosca Quarti-Trevano[12], Veikko Salomaa[1], Susana Sans[24], Carsten Oliver Schmidt[20], Ben Schöttker[5, 6], Stefan Söderberg[2], Abdonas Tamosiunas[19], Barbara Thorand[21, 22], Hugh Tunstall-Pedoe[25], Diego Vanuzzo[26], Giovanni Veronesi[7], Mark Woodward[27, 28], Karim Lekadir[29], Teemu Niiranen[1, 30]

[1] Department of Public Health and Welfare, Finnish Institute for Health and Welfare (THL), Helsinki, Finland

[2] Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

[3] Inserm, Institut Pasteur de Lille, Lille, France

[4] Department of Epidemiology and Public Health, University of Strasbourg, Strasbourg, France

[5] Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany

[6] Network Aging Research, Heidelberg University, Heidelberg, Germany

[7] Research center in Epidemiology and Preventive Medicine (EPIMED), Department of Medicine and Surgery, University of Insubria, Varese, Italy

[8] Department of Cardiovascular, Endocrine-metabolic Diseases and Aging, Istituto Superiore di Sanità, Rome, Italy

[9] Department of Epidemiology, Cardiovascular Disease Prevention and Heart Promotion, National Institute of Cardiology, Warsaw, Poland

[10] Lazarski University, Warsaw, Poland

[11] Department of Cardiology, Toulouse University School of Medicine, Rangueil Hospital, INSERM UMR 1027, Toulouse Cedex 9, France

[12] Clinica Medica, University of Milano-Bicocca, Milan, Italy

[13] Department of Community Medicine, UiT the Arctic University of Norway, Tromsø, Norway

[14] Department of Epidemiology and Prevention, IRCCS Neuromed, Pozzilli, Italy

[15] Research Center in Epidemiology and Preventive Medicine—EPIMED, Department of Medicine and Surgery, University of Insubria, Varese, Italy

[16] Center for Clinical Research and Prevention, Copenhagen University Hospital - Bispebjerg and Frederiksberg, Copenhagen, Denmark

[17] Centre for Public Health, The Queen's University of Belfast, Northern Ireland

[18] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

[19] Institute of Cardiology, Lithuanian University of Health Sciences, Kaunas, Lithuania

[20] Unit Quality in the Health Sciences (QIHS), Department SHIP-KEF, Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany

[21] Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Germany

[22] Institute for Medical Information Processing, Biometry and Epidemiology, Medical Faculty, Ludwig-Maximilians-Universität München, Munich, Germany

[23] German Center for Cardiovascular Disease Research (DZHK), partner site Munich Heart Alliance, Munich, Germany

[24] Catalan Department of Health, Barcelona, Spain

[25] Cardiovascular Epidemiology Unit, Institute of Cardiovascular Research, University of Dundee, Dundee, Scotland, UK

[26] MONICA-FRIULI Study Group, Udine, Italy

[27] The George Institute for Global Health, School of Public Health, Imperial College London, London UK

[28] The George Institute for Global Health, University of New South Wales, Sydney, Australia

[29] Artifcial Intelligence in Medicine Lab (BCN AIM), Departament de Matemàtiques i Informàtica, Universitat de Barcelona, Barcelona, Spain

[30] Department of Internal Medicine, University of Turku and Turku University Hospital, Turku, Finland

Corresponding author: Jaakko Reinikainen, email: jaakko.reinikainen@thl.fi, postal address: P.O. Box 30, FI-00271 Helsinki, Finland

Word count (including references): 4490

Abstract

Aims The regional and temporal differences in the associations between cardiovascular disease (CVD) and its classic risk factors are unknown. The current study examined these associations in different European regions over a 30-year period.

Methods The study sample comprised 553818 individuals from 49 cohorts in 11 European countries (baseline: 1982–2012) who were followed up for a maximum of 10 years. Risk factors (sex, smoking, diabetes, non-HDL [high-density lipoprotein] cholesterol, systolic blood pressure [BP], and body mass index [BMI]) and CVD events (coronary heart disease or stroke) were harmonized across cohorts. Risk factor-outcome associations were analysed using multivariable-adjusted Cox regression models, and differences in associations were assessed using meta-regression.

Results The differences in the risk factor-CVD associations between central Europe, northern Europe, southern Europe, and the United Kingdom were generally small. Men had a slightly higher hazard ratio (HR) in southern Europe (p=0.043 for overall difference) and those with diabetes had a slightly lower HR in central Europe (p=0.022 for overall difference) compared with the other regions. Of the six CVD risk factors, minor HR decreases per decade were observed for non-HDL cholesterol (7% per mmol/L; 95% confidence interval [CI], 3–10%) and systolic BP (4% per 20 mmHg; 95% CI, 1–8%), while a minor HR increase per decade was observed for BMI (7% per 10 kg/m^2; 95% CI, 1–13%).

Conclusion The results demonstrate that all classic CVD risk factors are still relevant in Europe, irrespective of regional area. Preventive strategies should focus on risk factors with the greatest population attributable risk.

Abstract word count: 250

Lay summary

All classic CVD risk factors are still relevant in Europe, irrespective of regional area.

- The differences in the associations of CVD risk factors with overt CVD between regions of Europe are generally small.
- Minor temporal hazard decreases were observed for non-HDL cholesterol and systolic blood pressure, while a minor hazard increase was observed for body mass index.

Keywords: Cardiovascular disease; Coronary heart disease; Stroke; Risk factor; Europe

Introduction

The association between cardiovascular disease (CVD) and its classic risk factors – that is, male sex, elevated blood pressure (BP), smoking, hyperlipidaemia, diabetes, and obesity – has been widely studied over the past 60 years (1,2). The identification of these risk factors has, in turn, led to considerable changes in the population-level lifestyle, the discovery of numerous pharmaceutical therapies, and a revolution in overall CVD care (3,4). As a consequence, the CVD mortality of working-age men and women has decreased by up to 80% in some European countries (5,6).

Considerable variation exists in the genetic structure and the lifestyle between various European regions (7,8). In addition, novel CVD risk factor therapies have been introduced over the past decades (3,4). Understanding the differences in the association between CVD risk factors and CVD outcomes in different European regions and over time are, therefore, critical for developing population-specific prevention and treatment strategies. However, due to a lack of harmonized data that span over several decades and that come from several regional areas, it is currently unknown, for example, whether the relative association between non-high-density lipoprotein (HDL) cholesterol and CVD is the same today as it was in the 1980s and whether systolic BP predisposes to CVD comparably in southern and northern Europe.

To elucidate the regional and temporal differences in the associations between CVD and its classic risk factors in Europe, we identified and harmonized cohorts that were recruited from general populations, spanning over three decades and including 553818 individuals from 49 cohorts and 11 European countries.

Methods

Study cohorts

This study included European cohorts from the Cardiovascular Research Data Catalogue (accessible via the European Society of Cardiology website at https://www.escardio.org/Research or via https://mica.eucanshare.bsc.es/) with baseline data from general population samples and with follow-up data on incident CVD. This resulted in 49 cohorts from 18 studies (see **Supplementary Table 1** for details of each study). Data from 16 of these studies had already been harmonized in the MORGAM (Monica Risk, Genetics, Archiving and Monograph) project (9). The two other studies were the Study of Health in Pomerania (SHIP) (10,11), specifically the SHIP-TREND cohort, and the UK Biobank (UKBB) (12). The combined data included participants from 11 European countries with baseline measurements in 1982–2012 and with follow-up extending up to 2021 (**Figure 1**).

In total, 710019 individuals were available for the study. Participants with history of coronary heart disease or stroke at baseline were excluded (N = 29965), as were those who did not have any follow-up data on coronary heart disease and stroke (N = 9850). Baseline age was restricted to 35 to 65 years, since this age range was covered by most of the cohorts, leading to an additional exclusion of 116386 individuals. After these exclusions, 553818 participants were included in the analyses.

CVD risk factors and outcomes

Smoking was defined as self-reported daily use of cigarettes, pipes, or cigar. Diabetes was defined as self-reported history of diabetes of any type. Systolic BP (mmHg), non-HDL cholesterol (mmol/L), and body mass index (BMI, kg/m^2) were measured at health examinations. All the datasets have made no distinction between sex and gender, so we could not separate them in this pooling project.

The outcome variables in the survival models were the first incident CVD event as well as its components – coronary heart disease (CHD; ICD-10: I20.0, I21, I22 for non-fatal and I21-I25, I46, R96, R98, R99 for fatal events) and stroke (ICD-10: I60, I61, I63, I64). Sensitivity analyses were carried out using a narrower definition of CHD (exclusion of sudden death, ICD-10: I46, R96, R98, R99). The follow-up time was restricted to ten years. CVD events at baseline were defined using register and questionnaire data, while CVD events during follow-up were defined using register or questionnaire data or using death certificates (clinically validated). Diagnostic criteria and data sources varied by cohort and year. Detailed information on recruitment, baseline examination, and follow-up and diagnostic procedures of each MORGAM cohort are available online (13).

Statistical methods

The individual-level data of the MORGAM and UKBB cohorts were fully accessible for the authors from the Finnish Institute for Health and Welfare. The SHIP-TREND cohort was analysed remotely using the DataSHIELD infrastructure (14) and its estimates were pooled with the estimates from the other cohorts using meta-analyses.

For the regional analyses, Europe was divided into four regions: central Europe (France, Germany, Lithuania, and Poland), northern Europe (Denmark, Finland, Norway, and Sweden), southern Europe (Italy and Spain) and the United Kingdom (UK). The years of examination and the region of each cohort are illustrated in **Figure 1**.

Risk factor-outcome associations were assessed by estimating hazard ratios (HR) from Cox proportional hazard models. The models were fitted separately for each cohort, using age as the timescale, and with sex, daily smoking, diabetes, systolic BP, non-HDL cholesterol, and BMI as covariates. Systolic BP, non-HDL cholesterol, and BMI were treated as continuous variables. Missing data from the MORGAM and UKBB cohorts, as detailed in **Table 1**, were handled by multiple imputation by generating ten

imputed datasets with random forest as the imputation method. Complete-case analyses were performed for the SHIP-TREND cohort because of technical restrictions of DataSHIELD. The proportional hazards assumption was checked by graphical inspection of Schoenfeld residuals, and no clear indications of violation were found.

Temporal and regional differences in the HRs were assessed by meta-analysing the cohort-level estimates using meta-regression with regional area and average baseline year (continuous) as covariates. These models were linear mixed-effects models with ln(HR) estimates of each risk factor as outcomes. The meta-regression parameters were estimated using restricted maximum likelihood. As the number of participants in the UKBB cohort was considerably greater than in the other cohorts, we also evaluated in sensitivity analyses whether the results were dominated by the greater weight of the UKBB by using meta-regression models with equal weight for each cohort. Additional sensitivity analyses were performed among the 458610 and 445103 individuals who did not use antihypertensive or lipid-lowering therapy at baseline, respectively (treatment data available for 543695 and 500153 participants, respectively).

All analyses were carried out with the R statistical software (version 4.2.1) (15). R-package metafor (16) was used for the meta-analyses, mice (17) for the multiple imputation, and survival (18) and dsSurvival (19) for the Cox models. A two-tailed p-value less than 0.05 was considered statistically significant.

Results

A total of 553818 participants were included in the analysis. Data on baseline characteristics and disease incidence by region of Europe are presented in

Table 1. The proportion of men in central Europe was higher than in the other regions, explained by the PRIME Study including only men. The relatively low share of smokers in the UK was due to the decreasing time-trends in smoking prevalence and the considerable weight of the UKBB (with baseline data from the 2000s only). Also, the lower CVD event rates in southern Europe and the UK reflected the later baseline examinations in these regions compared to central and northern Europe. The proportion of individuals with missing data was very small, except for non-HDL cholesterol (11.8%). The characteristics of participants by cohort are presented in **Supplementary Table 2**. **Figure 1** shows that the baseline examinations spanned from 1982 to 2012 and that the period from 1984 to 2009 was included in all four regions.

Men had a slightly higher HR of CVD in southern Europe (p=0.043 for overall difference) and those with diabetes had a slightly lower HR of CVD in central Europe (p=0.022 for overall difference) compared with corresponding participants in the other regions (**Figure 2**). The results were similar for CHD (**Figure 3**), while there were no clear regional differences for stroke (**Figure 4**). There was no evidence of regional differences when the narrow definition of CHD was used in a sensitivity analysis (**Supplementary Figure 1**).

Of the six CVD risk factors, minor temporal changes in the HRs for CVD were observed for BMI, systolic BP, and non-HDL cholesterol (**Figure 5**). The HR of BMI increased per decade by 7% (for each 10 kg/m^2), and the HRs of systolic BP and non-HDL cholesterol decreased per decade by 4% (for each 20 mmHg) and 7% (for each 1 mmol/L), respectively. Similar temporal changes for the HRs of BMI and non-HDL cholesterol were observed for CHD (**Supplementary Figure 2**), while for the narrow definition

of CHD, the HR of smoking was observed to increase over time (**Supplementary Figure 3**). With respect to stroke, the only clear temporal change was a decrease for the HR of systolic BP (**Supplementary Figure 4**). In the sensitivity analyses that were restricted to individuals who did not use antihypertensive or lipid-lowering therapy at baseline, the temporal trends for the HRs of systolic BP and non-HDL cholesterol were slightly attenuated (**Supplementary Figure 5**).

Results from unweighted analyses indicated that the results were not driven by the considerable weight of the UKBB (**Supplementary Figures 6-13**). The estimates from the meta-analyses that did not adjust for the region of Europe or the calendar year of examination (**Supplementary Table 3)** showed that, overall, all of the studied risk factors were positively associated with each of the outcomes, except that there was no evidence of an association between non-HDL cholesterol and stroke.

Discussion

This study, which used data from 49 cohorts that were recruited from general populations, showed that the regional and temporal differences in the association of CVD with its classic risk factors in Europe have been small. Some statistically significant differences were observed, but on an absolute scale they were minor. These results highlight that the relative associations between CVD and its risk factors are, in general, as relevant today as they were 40 years ago and that they exist in all regions of Europe.

Considerable regional differences exist in the burden of CVD and its risk factors. Within Europe, there is a clear north-east to south-west gradient in CVD mortality (20). Until now, multilevel analyses that combine individual-level data to assess the regional differences in relative, instead of absolute, risks of CVD have been lacking. Therefore, despite differences in absolute risks, it has remained unclear whether some risk factors could be more important than other risk factors in, for example, northern versus southern Europe, between which there are considerable differences in the populations' genetic structure and the implementation of CVD therapy (7,21). We observed only minor regional differences for sex in southern Europe and for diabetes in central Europe. The former observation could be a result of a gender health gap, pronounced at the expense of women, particularly in southern Europe (22). In addition, some of the countries from central Europe in our study, such as Poland and Lithuania, have some of the highest proportions of individuals with undiagnosed diabetes in Europe, which might have biased our findings (23). Some of these differences could also be explained by the between-country and between-region differences in diagnostics that could lead to misclassification of individuals with, for example, diabetes or CVD. However, in general, our results suggest that the classic risk factors are similarly linked to CVD outcomes in most parts of Europe. Therefore, preventive strategies for CVD should be similar in all parts of Europe and be focused on the risk factors with the greatest population attributable fraction. The population attributable fractions for BMI, systolic BP, non-HDL, smoking, and diabetes were recently reported to vary considerably by global geographic region, although less so on

an aggregated level within Europe (ranging from 53.2 to 55.8% in western Europe and from 57.6 to 60.2% in eastern Europe) (24).

The association of non-HDL cholesterol and systolic BP with CVD outcomes changed slightly over the study period. Namely, we observed a 7% decrease in the HR of non-HDL cholesterol (for each 1 mmol/L and decade) and 4% decrease in the HR of systolic BP (for each 20 mmHg and decade). However, the baseline examinations in our study were performed between 1982 and 2012. During this time, antihypertensive and lipid-lowering therapies have become more common and more effective, particularly among individuals with greatly elevated BP or lipid concentrations (25,26), which, most likely, explains the diminished association between these two risk factors and CVD outcomes over time (as was also suggested by our sensitivity analysis performed in participants untreated with such therapies at baseline). Furthermore, these results could be even more biased, given that we did not have information on drug therapy initiated during follow-up. The temporal changes of non-HDL cholesterol and systolic BP for the combined CVD endpoint could also be related to a change in the CHD/stroke-ratio across populations and over time. However, the direction of change was similar when CHD and stroke were analysed as separate outcomes. All in all, despite these minor temporal changes, our results highlight the importance of active and continued prevention and treatment of the classic CVD risk factors in Europe as none of them have lost their importance.

The relative importance of obesity with respect to CVD incidence increased slightly over the study period, as we observed a 7% increase in the HR per 10 kg/m^2 and decade. Combined with the fact that one in two adults in Europe is now overweight or obese (27), this finding raises an alarm on the dire consequences of obesity on cardiovascular health. The underlying causes of the temporal changes in the relative association between BMI and CVD are unknown. One of the main limitations of BMI is that it does not measure body composition, meaning that individuals with the same BMI can have considerable differences in fat mass and muscle mass. Prior studies have reported that obesity may

result in loss of muscle mass and muscle strength, which is commonly accompanied by a reduction in physical activity and an increase in metabolic disorders (28). At the same time, sarcopenic obesity may also have a synergistic effect on the development of CVD (29,30). In addition to lifestyle changes, preventive strategies might need to focus even more on weight control via the use of GLP-1 receptor antagonists and SGLT-2 inhibitors or via bariatric surgery, which have all been shown to reduce CVD events in individuals with diabetes or obesity (31–33).

The meta-data of the cohorts and variables used in this study are available from the Cardiovascular Research Data Catalogue (https://www.escardio.org/Research or https://mica.eucanshare.bsc.es/). This catalogue facilitates multicohort analyses by improving the discoverability and reuse of data. In the future, the role of the catalogue might be even greater, as new studies are continuously added to the catalogue and the data collection is still ongoing in some studies. Data used in separate publications, based on results from individual studies, are usually insufficiently harmonized to provide meaningful comparisons of the HRs. Thus, analyses that utilize harmonized individual-level data are preferred.

The major strength of this meta-analysis was the availability of individual-level data from several European countries and that spanned over multiple decades. In addition, the harmonized definitions of CVD risk factors and CVD outcomes increased the validity of our analysis. However, our study also has limitations. First, although the disease end-points were harmonized to the best possible standard, the diagnostics of CVD have evolved over the years with the introduction of more accurate imaging and biomarkers, which may have affected the results. Second, data were not available from all European countries and some cohorts represented only relatively small sub-regions within countries. Finally, due to a lack of direct measurements in the study samples, we could not perform analyses for LDL cholesterol, triglycerides, and other lipid subgroups.

In conclusion, our results demonstrate that all classic CVD risk factors are still relevant in Europe, irrespective of regional area and despite the temporal changes in CVD risk factor therapies. These findings may allow policy makers and future guidelines to more precisely "tailor" the preventive strategies in the current point in time. Our results also highlight that a continued monitoring of CVD and its classic risk factors is equally important in all parts of Europe and that the CVD burden may become more manageable if the preventive focus is on risk factors with the highest population attributable risk.

Acknowledgements

This research has been conducted using data from UK Biobank (Project ID 91128), a major biomedical database (www.ukbiobank.ac.uk).

Funding

This work was funded by the European Union's Horizon 2020 research and innovation program under grant agreement no. 825903 (euCanSHare project).

The MORGAM Project has received funding from EU projects MORGAM (Biomed, BMH4-CT98-3183), GenomEUtwin (FP5, QLG2-CT-2002-01254), ENGAGE (FP7, HEALTH-F4-2007-201413), CHANCES (FP7, HEALTH-F3-2010-242244), BiomarCaRE (FP7, HEALTH-F2-2011-278913), euCanSHare (Horizon 2020, No. 825903) and AFFECT-EU (Horizon 2020, No. 847770); and Medical Research Council, London (G0601463, No. 80983: Biomarkers in the MORGAM Populations). This has supported central coordination, workshops, and part of the activities of the MORGAM Data Centre, the MORGAM Laboratories and the MORGAM Participating Centers.

The KORA study was initiated and financed by the Helmholtz Zentrum München – German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research (BMBF) and by the State of Bavaria. Data collection in the KORA study is done in cooperation with the University Hospital of Augsburg. SHIP is part of the Community Medicine Research net of the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research

(grants no. 01ZZ9603, 01ZZ0103, and 01ZZ0403), the Ministry of Cultural Affairs as well as the Social Ministry of the Federal State of Mecklenburg-West Pomerania, and the network 'Greifswald Approach to Individualized Medicine (GANI_MED)' funded by the Federal Ministry of Education and Research (grant 03IS2061A). TN was funded by the Finnish Foundation for Cardiovascular Research, the Sigrid Jusélius Foundation and the Academy of Finland (grants n:o 321351 and 354447).

Conflict of interest

MW has done consultancy work for Amgen and Freeline in last 3 years. VS has had research collaboration with Bayer Ltd (unrelated to the present study). All other authors declare no conflict of interest.

Authors' Contributions

JR, KK, and TN contributed to the conception and design of the work. JR and JM harmonized the cohort data. JR conducted the statistical analyses with contribution of KK and TN. JR and TN drafted the manuscript. All the authors contributed to the interpretation of the results, made critical revision of the manuscript drafts, and gave final approval. JR and TN had full access to all data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data availability statement

The MORGAM data are not available in a public repository. Access to the data is restricted by the ethical approvals and the legislation of the European Union and the countries of each study. Approval by the Principal Investigator of each cohort study and the MORGAM Steering Group will be required for release of the data. The MORGAM Manual at https://www.thl.fi/publications/morgam/manual/contents.htm gives more information on access. Access information for the UKBB data can be found at https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access and for the SHIP data at https://transfer.ship-med.uni-greifswald.de/FAIRequest/?lang=en.

Ethical approval

The UKBB resource was approved by the UKBB Research Ethics Committee, and all participants provided written informed consent to participate. SHIP-TREND was approved by the ethics committee of the University of Greifswald and all participants were informed about the study protocol and signed the informed consent and the privacy statement. The included studies from the MORGAM project have been approved by local ethic committees. FINRISK cohorts 1982 and 1987: no ethics approval required for observational studies, but there is a law which allows the use of these data for public health research.

References

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020 Dec 22;76(25):2982–3021.

2. Mahmood SS, Levy D, Vasan RS, Wang TJ. The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. Lancet Lond Engl. 2014 Mar 15;383(9921):999–1008.

3. Mack MJ, Squiers JJ, Lytle BW, DiMaio JM, Mohr FW. Myocardial Revascularization Surgery: JACC Historical Breakthroughs in Perspective. J Am Coll Cardiol. 2021 Jul 27;78(4):365–83.

4. Canfield J, Totary-Jain H. 40 Years of Percutaneous Coronary Intervention: History and Future Directions. J Pers Med. 2018 Oct 1;8(4):33.

5. Jousilahti P, Laatikainen T, Salomaa V, Pietilä A, Vartiainen E, Puska P. 40-Year CHD Mortality Trends and the Role of Risk Factors in Mortality Decline: The North Karelia Project Experience. Glob Heart. 2016 Jun;11(2):207–12.

6. Mensah GA, Wei GS, Sorlie PD, Fine LJ, Rosenberg Y, Kaufmann PG, et al. Decline in Cardiovascular Mortality: Possible Causes and Implications. Circ Res. 2017 Jan 20;120(2):366–80.

7. Nelis M, Esko T, Mägi R, Zimprich F, Zimprich A, Toncheva D, et al. Genetic structure of Europeans: a view from the North-East. PloS One. 2009;4(5):e5472.

8. Astrup A. Healthy lifestyles in Europe: prevention of obesity and type II diabetes by diet and physical activity. Public Health Nutr. 2001 Apr;4(2B):499–515.

9. Evans A, Salomaa V, Kulathinal S, Asplund K, Cambien F, Ferrario M, et al. MORGAM (an international pooling of cardiovascular cohorts). Int J Epidemiol. 2005 Feb 1;34(1):21–7.

10. Völzke H, Alte D, Schmidt CO, Radke D, Lorbeer R, Friedrich N, et al. Cohort profile: the study of health in Pomerania. Int J Epidemiol. 2011 Apr;40(2):294–307.

11. Völzke H, Schössow J, Schmidt CO, Jürgens C, Richter A, Werner A, et al. Cohort Profile Update: The Study of Health in Pomerania (SHIP). Int J Epidemiol. 2022 Dec 13;51(6):e372–83.

12. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015 Mar;12(3):e1001779.

13. Kulathinal S, Niemelä M, Niiranen T, Saarela O, Palosaari T, Tapanainen H, et al. Description of MORGAM Cohorts [Internet]. National Institute for Health and Welfare, Finland; 2005 [cited 2023 May 19]. Available from: https://www.thl.fi/publications/morgam/cohorts/index.html

14. Gaye A, Marcon Y, Isaeva J, LaFlamme P, Turner A, Jones EM, et al. DataSHIELD: taking the analysis to the data, not the data to the analysis. Int J Epidemiol. 2014 Dec;43(6):1929–44.

15. R: The R Project for Statistical Computing [Internet]. [cited 2023 May 19]. Available from: https://www.r-project.org/

16. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. J Stat Softw. 2010 Aug 5;36:1–48.

17. Buuren S van, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. J Stat Softw. 2011 Dec 12;45:1–67.

18. Therneau TM, Grambsch PM. The Cox Model. Springer; 2000.

19. Banerjee S, Sofack GN, Papakonstantinou T, Avraam D, Burton P, Zöller D, et al. dsSurvival: Privacy preserving survival models for federated individual patient meta-analysis in DataSHIELD. BMC Res Notes. 2022 Jun 3;15(1):197.

20. Müller-Nordhorn J, Binting S, Roll S, Willich SN. An update on regional variation in cardiovascular mortality within Europe. Eur Heart J. 2008 May;29(10):1316–26.

21. Banegas JR, López-García E, Dallongeville J, Guallar E, Halcox JP, Borghi C, et al. Achievement of treatment goals for primary prevention of cardiovascular disease in clinical practice across Europe: the EURIKA study. Eur Heart J. 2011 Sep;32(17):2143–52.

22. Schmitz A, Lazarevič P. The gender health gap in Europe's ageing societies: universal findings across countries and age groups? Eur J Ageing. 2020 Dec;17(4):509–20.

23. International Diabetes Federation. IDF Diabetes Atlas | Tenth Edition [Internet]. [cited 2023 Apr 17]. Available from: https://diabetesatlas.org/

24. Global Cardiovascular Risk Consortium, Magnussen C, Ojeda FM, Leong DP, Alegre-Diaz J, Amouyel P, et al. Global Effect of Modifiable Risk Factors on Cardiovascular Disease and Mortality. N Engl J Med. 2023 Oct 5;389(14):1273–85.

25. Pedersen TR. The Success Story of LDL Cholesterol Lowering. Circ Res. 2016 Feb 19;118(4):721–31.

26. Saklayen MG, Deshpande NV. Timeline of History of Hypertension Treatment. Front Cardiovasc Med. 2016;3:3.

27. Stival C, Lugo A, Odone A, van den Brandt PA, Fernandez E, Tigova O, et al. Prevalence and Correlates of Overweight and Obesity in 12 European Countries in 2017-2018. Obes Facts. 2022;15(5):655–65.

28. Wannamethee SG, Atkins JL. Muscle loss and obesity: the health implications of sarcopenia and sarcopenic obesity. Proc Nutr Soc. 2015 Nov;74(4):405–12.

29. Stephen WC, Janssen I. Sarcopenic-obesity and cardiovascular disease risk in the elderly. J Nutr Health Aging. 2009 May;13(5):460–6.

30. Atkins JL, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG. Sarcopenic obesity and risk of cardiovascular disease and mortality: a population-based cohort study of older men. J Am Geriatr Soc. 2014 Feb;62(2):253–60.

31. Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol. 2021 Oct;9(10):653–62.

32. McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, et al. Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis. JAMA Cardiol. 2021 Feb 1;6(2):148–58.

33. van Veldhuisen SL, Gorter TM, van Woerden G, de Boer RA, Rienstra M, Hazebroek EJ, et al. Bariatric surgery and cardiovascular disease: a systematic review and meta-analysis. Eur Heart J. 2022 May 21;43(20):1955–69.

Figure legends

Figure 1 Baseline years of the studies. Separate lines within a study represent different cohorts. The cohorts of the PRIME Study are on different rows, as they were from two regions and have overlapping baseline years.

Figure 2 Hazard ratios (HR) with 95% confidence intervals (CI) for the risk factors on CVD from cohort-level meta-regression models adjusted for baseline year. The *p*-values are for overall differences between the regions.

Figure 3 Hazard ratios (HR) with 95% confidence intervals (CI) for the risk factors on coronary heart disease from cohort-level meta-regression models adjusted for baseline year. The *p*-values are for overall differences between the regions.

Figure 4 Hazard ratios (HR) with 95% confidence intervals (CI) for the risk factors on stroke from cohort-level meta-regression models adjusted for baseline year. The p-values are for overall differences between the regions.

Figure 5 Temporal trends in the hazard ratios of the risk factors on CVD. The slope parameters b (confidence interval) describe multiplicative change in HR in 10 years, p-values are for the null hypothesis of no change (b = 1) over time. Shapes of the symbols refer to the region (circle = central Europe, square = northern Europe, diamond = southern Europe, triangle = UK). The HRs of BMI are per each 10 kg/m^2, systolic blood pressure per each 20 mmHg, and non-HDL cholesterol per each 1 mmol/L.

Tables

Table 1 Baseline characteristics and disease events of the participants, age range 35-65 years.

	Central Europe	Northern Europe	Southern Europe	UK	All	Missing, n (%)
N	30248	55799	37056	430715	553818	
Men, n (%)	18373 (60.7)	27014 (48.4)	17728 (47.8)	192162 (44.6)	255277 (46.1)	0 (0.0)
Age, mean (sd)	52.4 (7.7)	48.5 (8.5)	50.0 (8.3)	54.4 (7.3)	53.4 (7.8)	0 (0.0)
Daily smoking, n (%)	7813 (26.3)	17188 (31.1)	9699 (26.7)	39767 (9.3)	74467 (13.6)	4282 (0.8)
Diabetes, n (%)	1443 (4.9)	1689 (3.1)	1467 (4.0)	18074 (4.2)	22673 (4.1)	4004 (0.7)
Systolic BP (mmHg), mean (sd)	134.6 (20.5)	135.5 (19.6)	135.4 (20.2)	136.3 (18.3)	136.0 (18.7)	1860 (0.3)
BMI (kg/m2), mean (sd)	27.4 (4.4)	26.3 (4.3)	27.4 (4.6)	27.3 (4.8)	27.2 (4.8)	3107 (0.6)
Non-HDL cholesterol (mmol/l), mean (sd)	4.4 (1.1)	4.6 (1.2)	4.2 (1.1)	4.3 (1.1)	4.3 (1.1)	64812 (11.8)
CVD, n (%)	1677 (5.0)	3401 (6.1)	742 (2.0)	11624 (2.7)	17444 (3.1)	0 (0.0)
CHD, n (%)	1219 (3.6)	2453 (4.4)	568 (1.5)	7244 (1.7)	11484 (2.0)	0 (0.0)
CHD (narrow definition)*, n (%)	990 (2.9)	2132 (3.8)	422 (1.1)	6954 (1.6)	10498 (1.9)	0 (0.0)
Stroke, n (%)	580 (1.7)	1104 (2.0)	216 (0.6)	4725 (1.1)	6625 (1.2)	0 (0.0)

sd, standard deviation; BP, blood pressure; BMI, body mass index; HDL, high-density lipoprotein; CVD, cardiovascular disease; CHD, coronary heart disease. *Without sudden death.

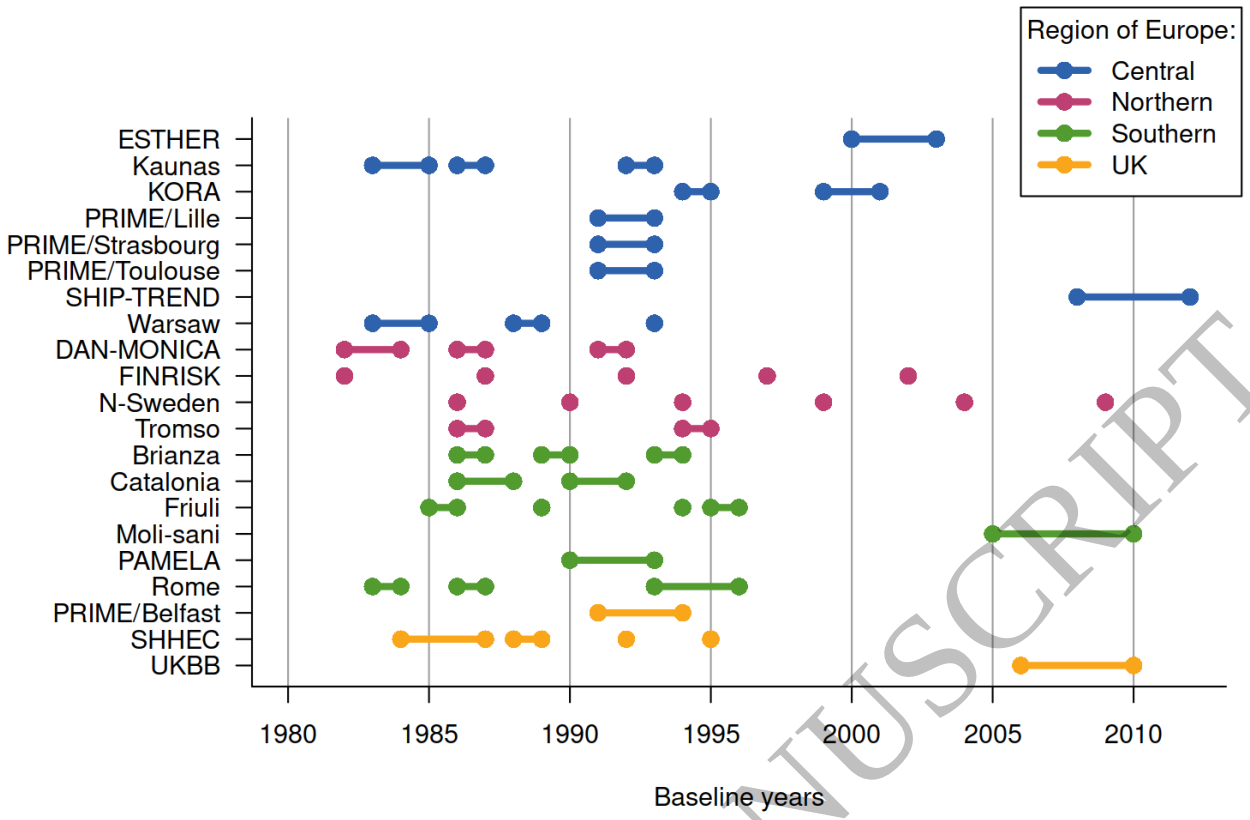


Figure 1 Baseline years of the studies. Separate lines within a study represent different cohorts. The cohorts of the PRIME Study are on different rows, as they were from two regions and have overlapping baseline years.

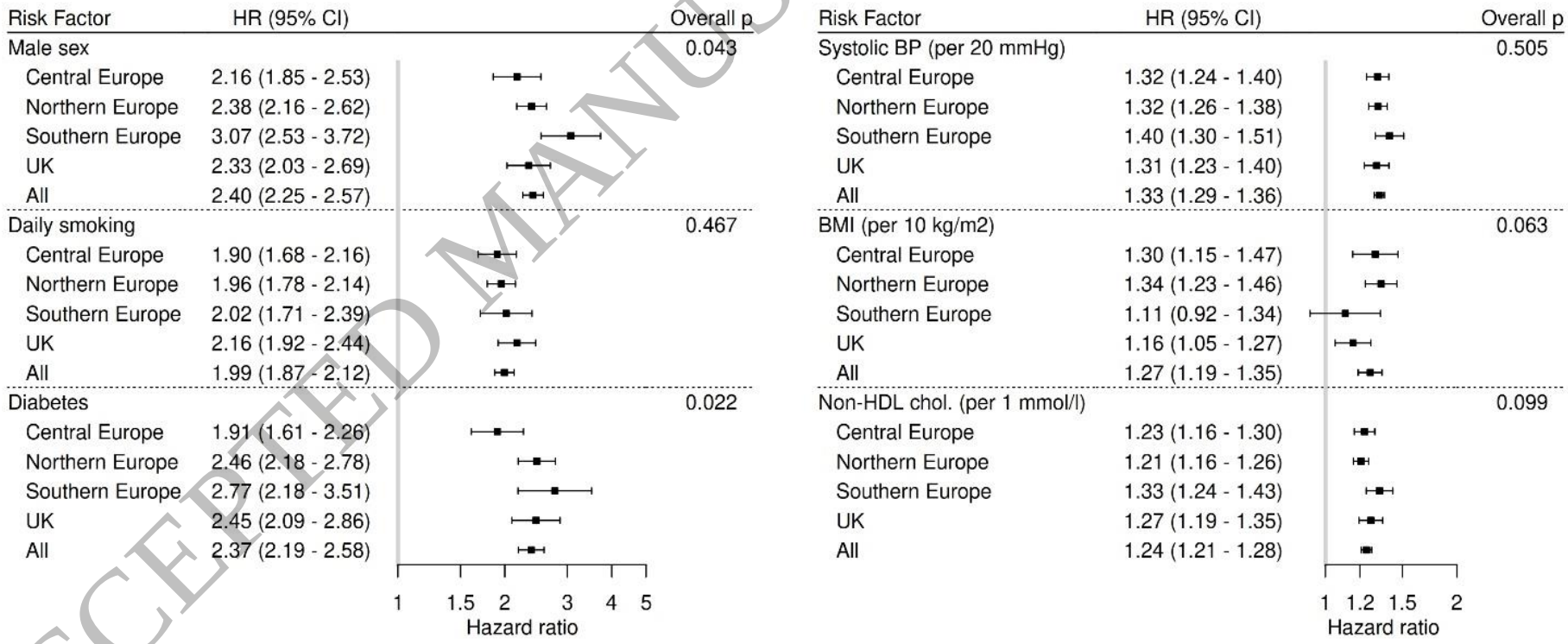


Figure 2 Hazard ratios (HR) with 95% confidence intervals (CI) for the risk factors on CVD from cohort-level meta-regression models adjusted for baseline year. The *p*-values are for overall differences between the regions.

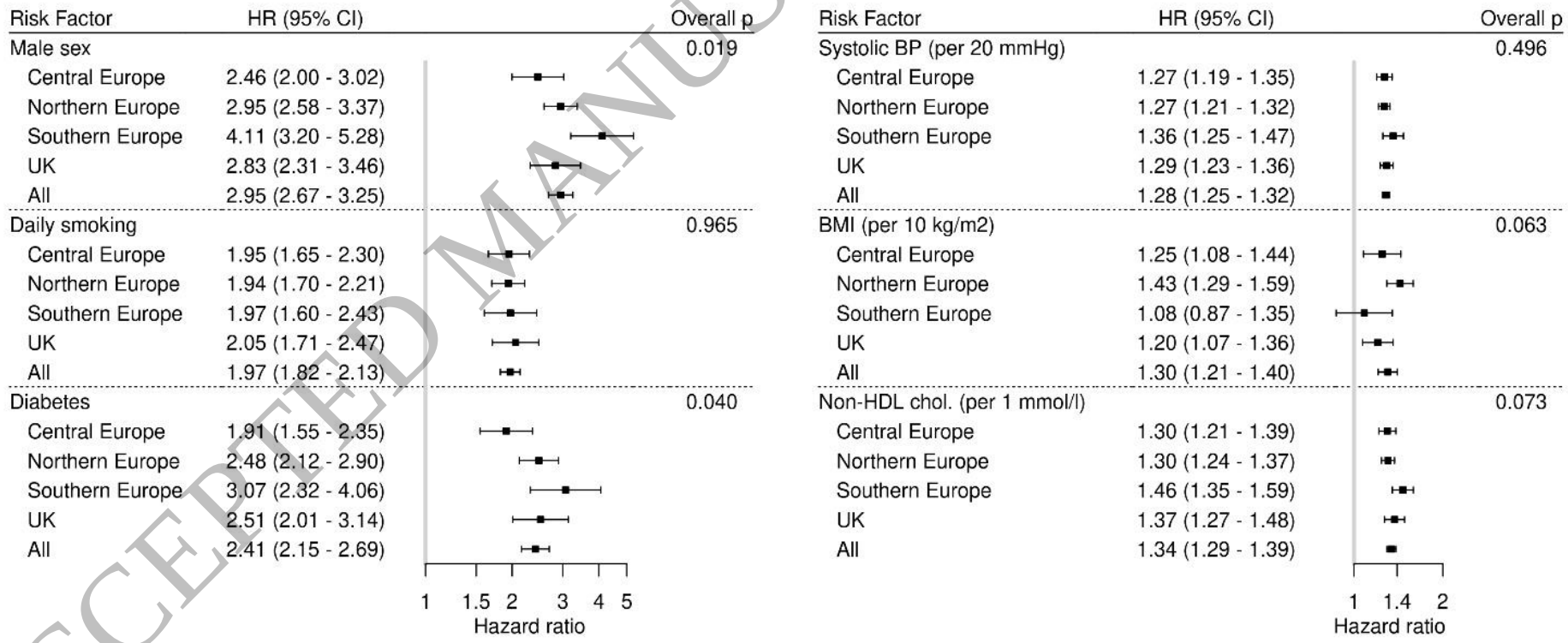


Figure 3 Hazard ratios (HR) with 95% confidence intervals (CI) for the risk factors on coronary heart disease from cohort-level meta-regression models adjusted for baseline year. The *p*-values are for overall differences between the regions.

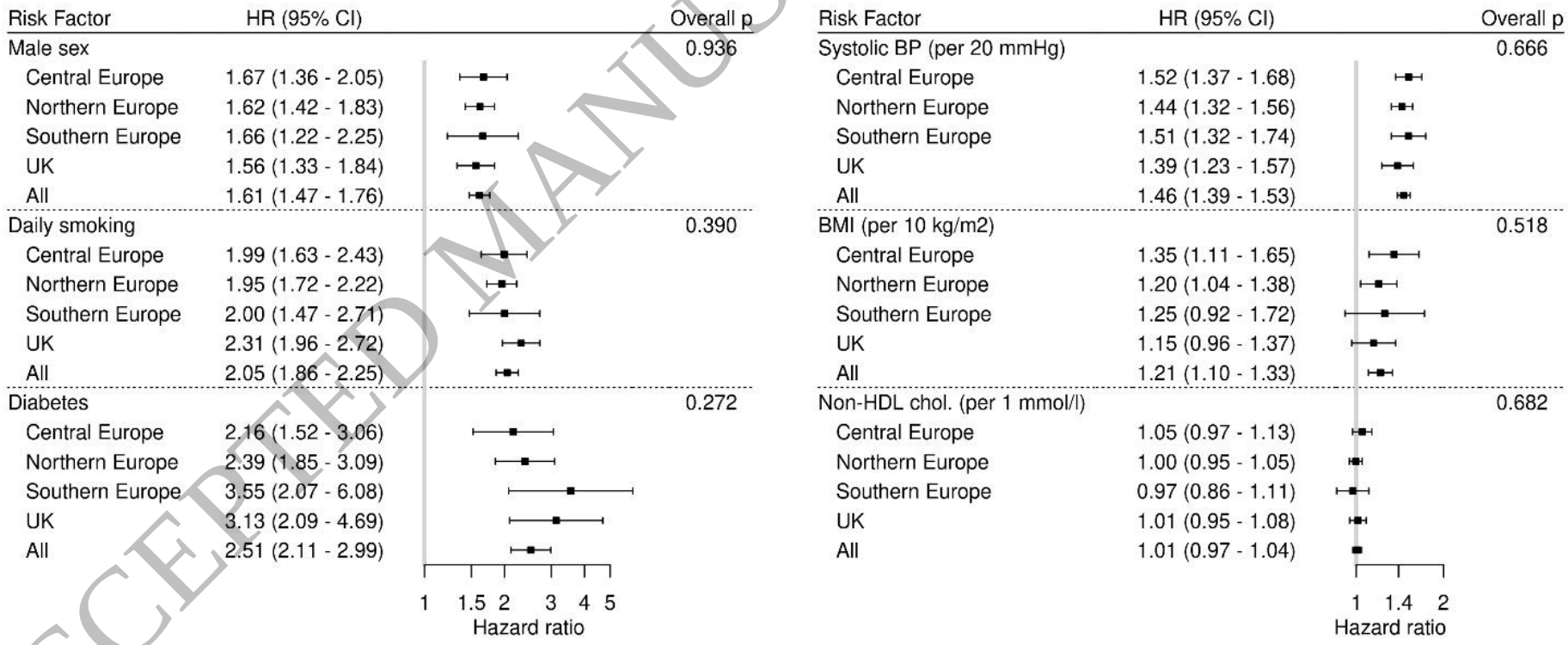


Figure 4 Hazard ratios (HR) with 95% confidence intervals (CI) for the risk factors on stroke from cohort-level meta-regression models adjusted for baseline year. The *p*-values are for overall differences between the regions.

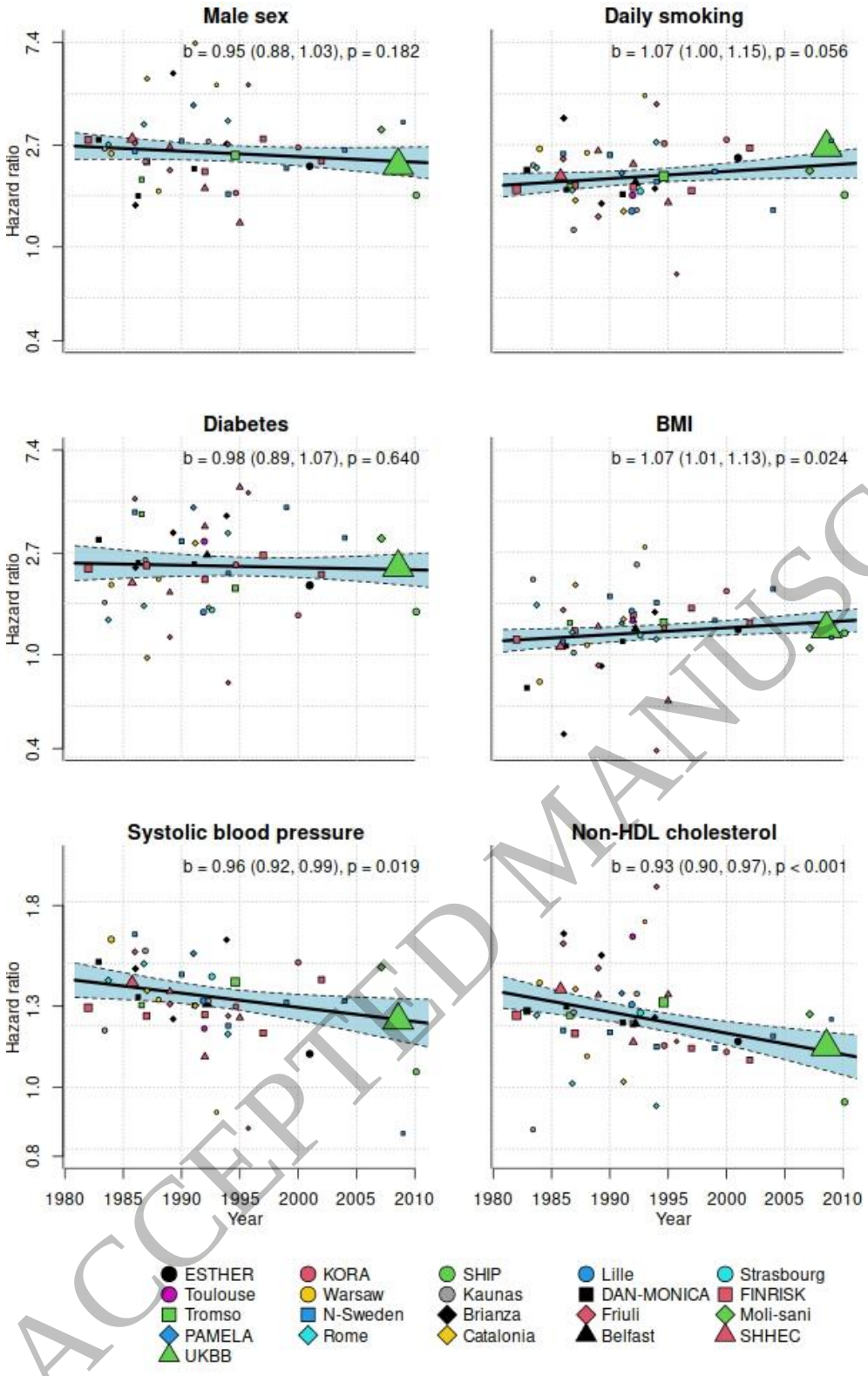


Figure 5 Temporal trends in the hazard ratios of the risk factors on CVD. The slope parameters *b* (confidence interval) describe multiplicative change in HR in 10 years, *p*-values are for the null hypothesis of no change (*b* = 1) over time. Shapes of the symbols refer to the region (circle = central

Europe, square = northern Europe, diamond = southern Europe, triangle = UK). The HRs of BMI are per each 10 kg/m^2, systolic blood pressure per each 20 mmHg, and non-HDL cholesterol per each 1 mmol

Key Question:

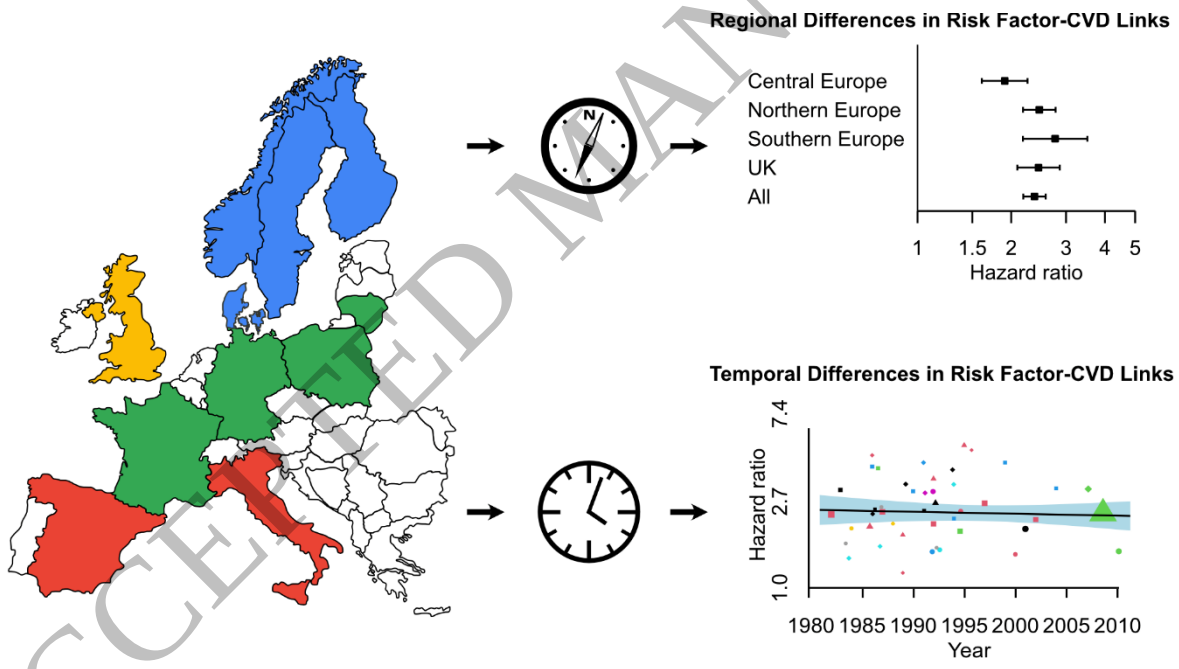
Have there been regional or temporal differences in the associations between cardiovascular disease (CVD) and its classic risk factors in Europe?

Key Finding:

The differences in the associations of CVD risk factors with overt CVD between regions of Europe are generally small. Minor temporal hazard decreases were observed for non-HDL cholesterol and systolic blood pressure, while a minor hazard increase was observed for body mass index.

Take-home Message:

All classic CVD risk factors are still relevant in Europe, irrespective of regional area. Preventive strategies should focus on risk factors with the greatest population attributable risk.



Graphical Abstract
155x85 mm (x DPI)