Impact of diet on ten-year absolute cardiovascular risk in a prospective cohort of 94 321 individuals: A tool for implementation of healthy diets

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Summary

Background An unhealthy diet is a major risk factor for cardiovascular disease attributing to the burden of non-communicable diseases. Current dietary guidelines are not sufficiently implemented and effective strategies to encourage people to change and maintain healthy diets are lacking. We aimed to evaluate the impact of incorporating dietary assessment into ten-year absolute risk charts for atherosclerotic cardiovascular disease (ASCVD).

Methods In the prospective Copenhagen General Population Study including 94 321 individuals, we generated sex-specific ten-year absolute risk scores for ASCVD according to adherence to dietary guidelines, using a short and valid food frequency questionnaire. To account for competing risk, we used the method of Fine-Gray.

Findings Non-adherence to dietary guidelines was associated with an atherogenic lipid and inflammatory profile. Ten-year absolute risk of ASCVD increased with increasing age, increasing systolic blood pressure, and decreasing adherence to dietary guidelines for both sexes. The highest ten-year absolute risk of ASCVD of 38% was observed in men aged 65–69 years who smoked, had very low adherence to dietary guidelines, and a systolic blood pressure between 160 and 179 mmHg. The corresponding value for women was 26%. Risk charts replacing dietary assessment with non-HDL cholesterol yielded similar estimates.

Interpretation Incorporation of a short dietary assessment into ten-year absolute risk charts has the potential to motivate patients to adhere to dietary guideline recommendations. Improved implementation of national dietary guidelines must be a cornerstone for future prevention of cardiovascular disease in both younger and older individuals.

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Keywords: Cardiovascular disease; Cohort study; Diet; Food-based dietary guidelines; Prevention; Risk charts

Introduction

Imbalanced and unhealthy diets are leading global risks to health and in particular to cardiovascular disease (CVD). Nearly 8 million deaths yearly are attributable to poor dietary habits,[1,2] and unhealthy diets are associated with increased lipid levels and atherosclerotic cardiovascular disease (ASCVD). Indeed, ischemic heart disease and stroke are the two major causes of disability in

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Research in context

Evidence before this study

Cardiovascular diseases take approximately 18 million lives each year making this group of disorders the leading cause of death worldwide. The most crucial behavioural risk factors are smoking, physical inactivity and importantly unhealthy diets. The effect of behavioural risk factors can lead to hypertension, diabetes, dyslipidaemia, and obesity. Better preventive measures are needed to avoid these risk factors and cardiovascular disease from occurring. Especially effective strategies to encourage people to change and maintain healthy diets are wanted. Risk charts for cardiovascular disease is a frequently used tool in the clinic to assess ten-year absolute risk for cardiovascular events. Our literature search revealed that the impact of incorporating dietary assessment into ten-year absolute risk charts for cardiovascular disease is unknown.

We searched PubMed database for articles published from January 1, 1980 to January 25, 2022 using the following search terms: "cardiovascular disease", "ischemic vascular disease", "atherosclerotic cardiovascular disease", "ischemic heart disease", "myocardial infarction", "ischemic cerebrovascular disease", "ischemic stroke", "peripheral arterial disease", "risk charts", "absolute risk", "diet*" and "nutrition*".

Added value of this study

To our knowledge this is the first study to investigate the impact of incorporating dietary assessment into ten-year absolute risk charts for cardiovascular disease. In a study of 94 321 individuals, we found that ten-year absolute risk charts for atherosclerotic cardiovascular disease showed similar results when either including dietary assessment or non-HDL cholesterol. Risk estimates in charts including dietary assessment were non-inferior to charts including non-HDL cholesterol in discrimination analyses. Using dietary assessment in risk charts may motivate the patient to adopt a healthy diet compared with charts based on cholesterol levels in the blood, which for some patients can be difficult to understand. Risk charts including dietary assessment could be an additional instrument for the clinician to use in general practice or in cardiology departments when determining a patient's risk of developing CVD or when discussing lifestyle habits.

Implications of all the available evidence

Incorporation of dietary assessment into ten-year absolute risk charts has the potential to convince patients to adhere to dietary guideline recommendations. Improved implementation of national dietary guidelines must be a cornerstone in prevention of cardiovascular disease and can also provide environmental benefits. Risk charts including a short dietary assessment can be a tool to change people's diet, not only to a healthier diet, but also to a more sustainable one.

individuals above age 50 years.[3] Therefore, the potential for prevention is substantial; however, current commitments to reduce morbidity and mortality from premature non-communicable disease are not met.[4] Applicable strategies to help implement adherence to dietary guidelines and to improve general public health are needed.

Unhealthy diets, smoking, high body-mass-index, physical inactivity, hypertension, hyperlipidaemia, diabetes mellitus and alcohol consumption have been identified as major metabolic and behavioural risk factors for CVD.[2] Trends in CVD incidence and prevalence reflect dietary patterns[5] and a focus on promoting healthy diets will contribute to lower rates of obesity hypertension, hyperlipidaemia and diabetes mellitus. A healthy diet is recommended as a cornerstone in CVD prevention with focus on replacing saturated fat with unsaturated fats, reducing salt intake, choosing a plant-based diet rich in fibres, eating fish frequently, and restricting the intake of processed meat as well as sugar-sweetened beverages.[6] A recent study suggests that better implementation of national dietary guidelines could be associated with an average reduction of 15% in premature mortality from diet related non-communicable diseases.[7] One of the biggest challenges in dietary prevention of CVD is to develop better strategies to encourage people to change their diets as well as to maintain them.

Updated charts for European populations (SCORE2) including older individuals (SCORE2-OP) provide risk prediction algorithms to estimate ten-year risk of fatal and non-fatal CVD using non-HDL (high-density lipoprotein) cholesterol, sex, smoking status, age, and systolic blood pressure.[8,9] Whether incorporation of dietary assessment into ten-year risk charts, instead of non-HDL cholesterol, yields useful risk predictions is unknown. Risk charts using dietary assessment may contribute to a targeted prevention strategy, improve implementation of dietary guidelines, and stimulate the individual to act and change dietary habits. However, short, and valid instruments for dietary assessment are crucial for the implementation of such strategies.

The primary aim of this study was to determine the impact of incorporating dietary assessment into sex-specific ten-year absolute risk charts for ASCVD. A secondary aim was to compare these risk estimates with the corresponding estimates obtained when replacing dietary assessment with non-HDL cholesterol as used in the recently updated European charts, SCORE2 and SCORE2-OP.[8,9]

Methods

All individuals in the studies gave written informed consent. Institutional review boards and a Danish Ethical Committee approved the studies (H-KF-01-144/01 and KF-100.2039/91), which were conducted according to the Declarations of Helsinki.

Setting and participants

The Copenhagen General Population Study (CGPS) is a prospective cohort study initiated in 2003 with ongoing enrolment until 2015 and with follow-up examinations starting thereafter.[10,11] Individuals from the greater Copenhagen area were randomly selected based on the national Danish Civil Registration System to reflect the adult Danish population aged 20–100 years. At baseline (study inclusion) each individual filled out an extensive questionnaire including a simple food frequency questionnaire (FFQ), which was reviewed together with an investigator on the day of attendance. A physical examination and blood samples including DNA extraction were also performed at study inclusion. Information on diet, vital status and disease status were available for 94 321 individuals. All individuals were white and of Danish descent. Follow-up was by linkage to the Danish registries with information on diagnosis codes, emigration status, and causes of death. End of follow-up was at occurrence of event, emigration (N=388), death (N=9 235) or on 7 December 2018 (last update of the registries), whichever came first.

The Copenhagen City Heart Study (CCHS) was initiated in 1976 with five follow-up examinations at approximately 10-year intervals. Participants were recruited and examined as in the CGPS. There was no overlap between participants. We included 5 385 individuals with dietary information available and participating in the fourth examination of the CCHS (2001–2003).

Dietary assessment

A simple FFQ (Supplementary Table 1) was filled out at baseline along with the extensive questionnaire in the CGPS. Both were subsequently reviewed together with an investigator to ensure validity of the answers. The FFQ focused on selected key items of the Danish food-based dietary guidelines. The guidelines' overall recommendations are to (1) eat plant-rich, varied, and not too much, (2) eat more vegetables and fruits, (3) eat less meat – choose legumes and fish, (4) eat whole grains (5) choose vegetable oils and low-fat dairy products, (6) eat less of the sweet, salty, and fatty, (7) quench your thirst in water.[12] The FFQ specifically explored the following: dietary fat quality in cold and warm meals (saturated fats: butter, butter-based blends, and hard margarines; unsaturated fats: soft margarines and vegetable oils), and usual intake frequencies (from almost never to several daily servings) of fruit, vegetables, fish, sugar-sweetened beverages, cold meat cuts like sausages and pâtés for open sandwiches, and fast food. The present FFQ closely resembles the Dietary Quality Score (DQS) which has been validated against an extensive 198 item FFQ. The DQS proved to be a reliable proxy for an overall healthy, average, or unhealthy diet.[13] The DQS was also associated with atherogenic lipid traits and a cardiovascular risk score.

FFQ-questions were classified into three levels of importance (from A to C) for an overall healthy dietary pattern, as previously described.[14] Class A questions focused on major contributors to the dietary macronutrient composition, specifically dietary fat quality (fats in cold and warm meals, unsaturated vs. saturated fat), and dietary fibre content (fruit ≥3 versus <3 weekly servings and vegetables ≥3 versus <3 weekly servings). Class B questions elucidated intake of specific foods considered healthy (fish ≥3 versus <1 weekly servings), or unhealthy (sugar sweetened beverages <0·5 versus ≥1 L/week). Class C questions focused on foods rich in salt (cold meat cuts like sausages and pâtés for open sandwiches <5 versus ≥7 weekly servings and fast foods <1 versus ≥1 weekly servings).[14]

Based on the answers in the FFQ's, individuals were divided into four predefined categories ranging from high to very low adherence to current dietary guidelines (Supplementary Figure 1 and Supplementary Table 2). High adherence: All class A, B and C answers in agreement with guidelines or all A, B, and C answers in agreement with guidelines except for either one class B answer in disagreement with guidelines, or one or two class C answers in disagreement with guidelines. Intermediate adherence: Individuals between high and low adherence categories. Low adherence: Two class A in disagreement with guidelines and one or two class B in disagreement with guidelines. Very low adherence: Three or four class A answers in disagreement with guidelines.

To evaluate changes in dietary patterns over time we used a subset of the cohort including 12 800 individuals. All individuals in the subset filled out the FFQ at both baseline (CGPS1) and at the follow-up (CGPS2) with a median time interval of 10 years.

Laboratory analyses

Total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, apolipoprotein B (apo B) and apolipoprotein A-1 (apoA1), high sensitivity C-reactive protein (hs-CRP), fibrinogen, α_1-antitrypsin, and leucocytes were measured on standard hospital biochemical equipment at baseline. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation when triglycerides were less than 4 mmol/L or otherwise measured directly.[15] Non-HDL cholesterol was total cholesterol minus HDL cholesterol. Remnant cholesterol was total cholesterol minus HDL cholesterol and LDL cholesterol. For individuals using lipid-lowering therapy, values for total cholesterol, LDL cholesterol, and triglycerides were multiplied by 1·16 (=1/(1-0·14)), 1·23 (=1/1-0·19) and 1·12 (=1/(1-0·11)), respectively, corresponding to average reductions of 14%, 19% and 11% using common statin treatment regimens.[16]

Endpoints

Endpoints included from the national registries were ischemic heart disease, cerebrovascular disease, and peripheral arterial disease. Endpoints were based on the World Health Organization's codes for International Classification of Diseases, Eighth Revision and Ten Revision (ICD-8 and ICD-10) and were collected from 1 January 1977 through 7 December 2018 (end of follow-up) by linkage to the national Danish Patient Registry as every hospital discharge diagnosis is recorded centrally. The national Danish Patient Registry has information on all patient contacts in Denmark including emergency wards and outpatient clinics. Diagnoses of ischemic heart disease including stable angina pectoris, unstable angina pectoris and myocardial infarction were ICD-8 codes 410-414, and ICD-10 codes I20-I25; cerebrovascular disease including ischemic cerebrovascular disease, ischemic stroke and haemorrhagic stroke was ICD-8 codes 431-438 and ICD-10 codes I160-I69, and G45; peripheral arterial disease was ICD-8 codes 440-414, 443·99 and 445, and ICD-10 codes I70-I72 and I73·9. Events before study inclusion included both ICD-8 and ICD-10 codes, whereas an event after baseline was based on ICD-10 codes only. In Denmark, ICD-9 codes were never used.

The national Danish Causes of Death Registry contains data on the causes of all deaths in Denmark. Information about death from CVD (ICD-8 codes 390–458 and ICD-10 codes I00–I99) was extracted from the Danish Registry of Causes of Death censored on 31 December 2016. All-cause mortality data were available up until 7 December 2018 (end of follow-up). Cardiovascular death was considered present if one of the top three ranked causes of death was cardiovascular. Information on births, deaths, emigrations, and immigrations was collected from the national Danish Civil Registration System.

The combined endpoint, ASCVD, included fatal- and non-fatal ischemic heart disease (including stable angina pectoris, unstable angina pectoris and myocardial infarction), ischemic cerebrovascular disease (including ischemic stroke) and peripheral arterial disease; whichever came first. CVD included both fatal and non-fatal myocardial infarction and stroke. Whichever occurrence came first was considered an event and thus end of follow-up. The CVD endpoint is equivalent to the endpoint used in the recently updated prediction models, SCORE2 and SCORE2-OP, to estimate ten-year absolute risk of CVD in Europe.[8,9]

Median follow-up time was from 8·5 years for ASCVD to 8·8 years for peripheral arterial disease (range for all endpoints: <1–15 years). The complete Danish registries ensure that no individuals were lost to follow-up.

Statistical methods

We used Stata/SE version 16.1 (Stata Corp, College Station, TX) and the Medflex package (v. 0·6-7) in R (v 3·6·1). Probability values <0·001 are given as powers of 10. We had 80% statistical power at a two-sided p<0·05 to detect a hazard ratio (HR) of 1·11 for ischemic heart disease, 1·12 for ischemic cerebrovascular disease, 1·17 for peripheral arterial disease, 1·09 for ASCVD, and 1·10 for CVD per increase in group of adherence to dietary guidelines. Kruskal-Wallis test was used to compare continuous covariates by dietary groups. To impute covariates with missing data, we used multiple imputation using age and sex in the model.[17] Exposure (dietary assessment) and endpoints were not imputed for missing data. Missing values were <1·10% for modifiable risk factors (Supplementary Table 3).

Assumptions of Cox proportional hazards including proportionality of hazards, linearity of effects, and absence of influential observations were checked by plotting −ln(-ln[survival]) versus ln(analysis time), by Martingale residuals, and by deviance residuals, respectively. There was no suspicion of non-proportionality, non-linearity of continuous covariates, or influence of outliers.

All analyses were conducted in individuals without the diagnosis of the investigated endpoint and diabetes mellitus. Cause-specific Cox proportional hazard regressions were used to examine the associations of dietary groups with all cardiovascular endpoints included. P for trend was not applied due to apparent non-linear associations. A significant p for trend can be misleading when a non-linear monotonical association is observed, since a linear model - the simplest monotonical function - will capture only part of the non-linear relationship. Regressions included age as underlying timescale (referred to as age adjustment) with delayed entry (left truncation at study examination) and with censoring at event, emigration (N=388), death (N=9 235) or end of follow-up. Adjustments were done in two steps: a simple model including adjustment for age and sex; and a second multivariable model adjusting for age, sex, household income, education, body mass index, physical activity in leisure time, smoking status, alcohol consumption, hypertension, lipid lowering therapy, and ischemic heart disease diagnosed before study entry. Household income, education, alcohol intake, smoking, physical activity, and lipid-lowing therapy were all self-reported at baseline and dichotomous. Low household income was defined as <400 000 DKK/year (<53 800 €/year). Low educational level was <8 years. High alcohol intake was >14/21 units of alcohol per week for women/men (1 unit alcohol ~ 12g). Smoking was current smoking. Physical inactivity was ≤4 h/week of light physical activity in leisure time. Lipid-lowering therapy was mainly statins (yes/no). Diabetes mellitus was self-reported disease, plasma glucose levels of more than 11mmol/L (>198mg/dL), medication prescribed for diabetes, and/or hospitalization due to diabetes (ICD-8 code 249, 250; ICD-10 code E10-11, E13-14) before baseline. Systolic blood pressure was measured at baseline

in mmHg. Hypertension was self-reported disease, systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90mmHg, and/or self-reported use of antihypertensive medication. Body mass index was calculated from measured weight in kilograms divided by measured height in meters squared and treated as a continuous covariate.

Incidence rates were events/person-years independent of the underlying distribution. Confidence intervals for the incidence rates were calculated using a jackknife estimation. Sensitivity analyses testing for reverse causation were conducted by excluding individuals with less than five years of follow-up. Further sensitivity analyses were performed to test whether main analyses were robust after additional adjustment for baseline age as a continuous covariate.

Interactions were tested between diet groups and each covariate (dichotomized) on risk of ASCVD. Interactions were calculated using an interaction term (diet group x covariate in two groups) in a multivariable adjusted model. P-values for interaction were obtained using the method by Altman and Bland.[18] First, we estimated HRs per one unit increase in non-adherence to dietary guidelines by using Cox proportional hazards regression models and presented for each group of the potentially interacting covariate. Second, we also plotted marginal effects of interaction terms from Cox proportional hazards regression illustrating predicted HRs for each group of adherence to dietary guidelines for different values of the interacting covariate. Stratified analyses were performed when significant interaction was observed.

Ten-year absolute risks of CVD or ASCVD were calculated based on Fine-Gray proportional sub-hazards models, which account for the possibility of death (from other causes) or emigration as competing events.[19] The same method was used in SCORE2, and we therefore chose this method to enable comparison between risk estimates.[8,9] Further, the Fine-Gray model is recommended when focusing on predicting prognosis or the absolute incidence of a disease in the presence of competing risks.[20] Models were sex-specific and included the following predictors: age, smoking status, systolic blood pressure, and dietary assessment. Subsequently, non-HDL cholesterol was used in the risk score charts instead of dietary assessment. Risk models were derived in participants aged 40-69 and 70-89 years. We calculated Harrell's C-index, adjusting for competing risks, to assess discrimination between those who developed a cardiovascular event with those who did not.[21] The index was estimated for both models and for CVD and ASCVD, respectively. With this method individuals experiencing a competing event are censored at infinity to indicate that they will never experience the event of interest, in this case CVD or ASCVD. A C-index around 0·5 indicates that prediction is random without any ability to discriminate. A C-index of 1 indicates perfect concordance. Furthermore, we estimated the area under the receiver operating characteristic (AUC-ROC) curve for the models using dietary assessment and non-HDL cholesterol.[22,23] Lastly, p-values for the difference in discrimination between models were calculated using the method by Altman and Bland.[18]

To estimate the effect of mediation through non-HDL cholesterol, the natural effects mediation model was used.[24] The mediated effect was calculated as the ratio between the indirect effect of non-HDL cholesterol and the total effect (the direct effect of diet + indirect effect of non-HDL cholesterol). The mediation design is further described in Supplementary Methods.

Lastly, we used the CCHS to calculate ten-year absolute risk estimates for ASCVD to validate our model in a comparable cohort.

Role of the funding source

The funding sources had no role in the study design, data collection, data analysis, interpretation, or writing of the manuscript.

Results

Table 1 shows baseline characteristics of the 94 321 individuals included in this study, stratified by four groups of adherence to dietary guidelines. Twenty-one percent (19 702/94 321) had high adherence to dietary guidelines, 62% (58 562/94 321) had intermediate adherence, 8% (7 437/94 321) had low adherence and 9% (8 620/94 321) had very low adherence to dietary guidelines. Individuals with low and very low adherence to dietary guidelines were more frequently men, had lower household incomes, shorter education, lower physical activity levels in leisure time, higher smoking rates and alcohol consumption, higher body mass index, higher rates of hypertension and were less frequently treated with lipid-lowering therapy.

Changes in diet over time

Just over half, 56% (7 223/12 800), did not change their dietary habits; 35% (4 435/12 800) only changed one group of adherence to dietary guidelines: e.g. from high adherence to intermediate adherence; 8% (1 070/12 800) changed two groups: e.g. from high adherence to low adherence; and only 0·6% (72/12 800) changed three groups: from high adherence to very low adherence or vice versa (Supplementary Figure 2).

Biochemistry

Lipids and lipoproteins. Levels of non-HDL cholesterol, apolipoprotein B, triglycerides, remnant cholesterol, total cholesterol, and LDL cholesterol were higher in individuals with intermediate, low and very low adherence to dietary guidelines than in those with high

Baseline characteristics	Adherence to dietary guidelines			
	High	Intermediate	Low	Very Low
N, % (no.)	21 (19 702)	62 (58 562)	8 (7 437)	9 (8 620)
Age, years	59·7 (50·8–67·4)	57·6 (47·6–67·2)	55·2 (45·8–65·8)	60·2 (49·0–70·2)
Men, % (no.)	34 (6 608)	45 (26 115)	56 (4 153)	66 (5 660)
Low household income, % (no.)	31 (6 177)	34 (19 922)	38 (2 845)	52 (4 491)
Education <8 years, % (no.)	7 (1 439)	9 (5 031)	11 (843)	18 (1 513)
Body mass index, kg/m^2	25·4 (23·1–28·1)	25·5 (23·1–28·3)	25·8 (23·3–28·8)	26·1 (23·5–29·2)
Physical inactivity in leisure time, % (no.)	40 (7 930)	47 (27 649)	56 (4 155)	65 (5 564)
Smoking, % (no.)	9 (1 736)	15 (8 791)	25 (1 869)	38 (3 294)
High alcohol consumption, % (no.)	16 (3 218)	17 (9 858)	16 (1 125)	23 (1 948)
Systolic blood pressure, mmHg	140 (126–155)	140 (126–155)	140 (126–154)	141 (129–156)
Hypertension, % (no.)	61 (11 929)	59 (34 783)	60 (4 445)	66 (5 685)
Diabetes mellitus, % (no.)	5 (938)	4 (2 350)	3 (252)	5 (410)
Lipid lowering therapy, % (no.)	15 (2 999)	12 (6 824)	9 (678)	12 (1 009)

***Table 1*: Characteristics of 94 321 individuals grouped according to degree of adherence to Danish dietary guidelines.**
Values are median (25th–75th centiles) or percentage (%) and are from the day of enrolment. Low household income was defined as <400 000 DKK/year (<53 800€/year). Low educational level was <8 years. Body mass index was calculated from measured weight in kilograms divided by measured height in meters squared. Physical inactivity was ≤4 h/week of light physical exercise in leisure time. Smoking was current smoking. High alcohol intake was >14/21 units of alcohol per week for women/men (1 unit alcohol ~ 12g). Systolic blood pressure was measured at baseline in mmHg. Hypertension was self-reported disease, systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90mmHg, and/or self-reported use of antihypertensive medication. Diabetes mellitus was self-reported disease, plasma glucose levels of more than 11mmol/L (>198mg/dL), medication prescribed for diabetes, and/or hospitalization due to diabetes (ICD-8 code 249, 250; ICD-10 code E10-11, E13-14) before baseline examination. Lipid-lowering therapy was mainly statins (yes/no).

adherence. The levels increased for each group towards very low adherence to dietary guidelines while HDL cholesterol and apoA1 levels decreased (p-values ranging from $<1\times10^{-300}$ to 4×10^{-19}) (Figure 1 and Supplementary Table 4).

Inflammatory markers. Levels of inflammatory markers including hs-CRP, fibrinogen, α_1-antitrypsin, and leucocytes increased for each group towards very low adherence to dietary guidelines (p-values ranging from 1×10^{-240} to 2×10^{-75}) (Supplementary Figure 3 and Supplementary Table 4).

Risk of atherosclerotic cardiovascular diseases

For the combined ASCVD endpoint, compared with individuals with high adherence to dietary guidelines (reference), age and sex adjusted HRs were 1·02 (95% confidence interval 0·94-1·10) for individuals with intermediate adherence, 1·22 (1·08-1·38) for low adherence, and 1·52 (1·.37-1·69) for individuals with very low adherence to dietary guidelines. Age and sex adjusted HRs for the individual diagnoses of ASCVD similarly increased with lower adherence to dietary guidelines with HRs ranging from 1·13-1·40 for individuals with low adherence and 1·32-2·22 for individuals with very low adherence to dietary guidelines (Figure 2). The association appeared non-linear. After multivariable adjustment results were largely similar (Figure 2). Sensitivity analyses excluding individuals with less than five years of follow-up showed similar results (Supplementary Figure 4). Analyses further adjusting for baseline age as a continuous covariate were also similar (data not shown).

Interactions were observed between dietary groups and sex (p=0·04) and smoking status ($p=1\times10^{-4}$) in a multivariable adjusted model on risk of ASCVD (Supplementary Figure 5) and was further illustrated by marginal plots, where risk estimates were stratified for each group of the exposure (Supplementary Figure 6). We therefore performed stratified analyses on sex and smoking status which showed similar results between groups (Supplementary Table 5). Further, stratified analyses on age and household income showed similar results between groups (Supplementary Table 5).

Ten-year absolute risk of CVD by dietary groups and non-HDL cholesterol

To ensure that absolute risks in CGPS were concordant with the recently published SCORE2 charts,[8,9] we first estimated ten-year absolute risks for the CVD endpoint as used in SCORE2. Estimates for non-HDL cholesterol in the present study were similar to SCORE2 (Figure 3, Supplementary Figure 7, Supplementary Results), and models including dietary assessment and non-HDL cholesterol performed similarly (Supplementary Table 6).

Ten-year absolute risk of ASCVD by dietary groups and non-HDL cholesterol

The highest ten-year absolute risk for men of 38% was seen in men aged 65-69 with very low adherence to

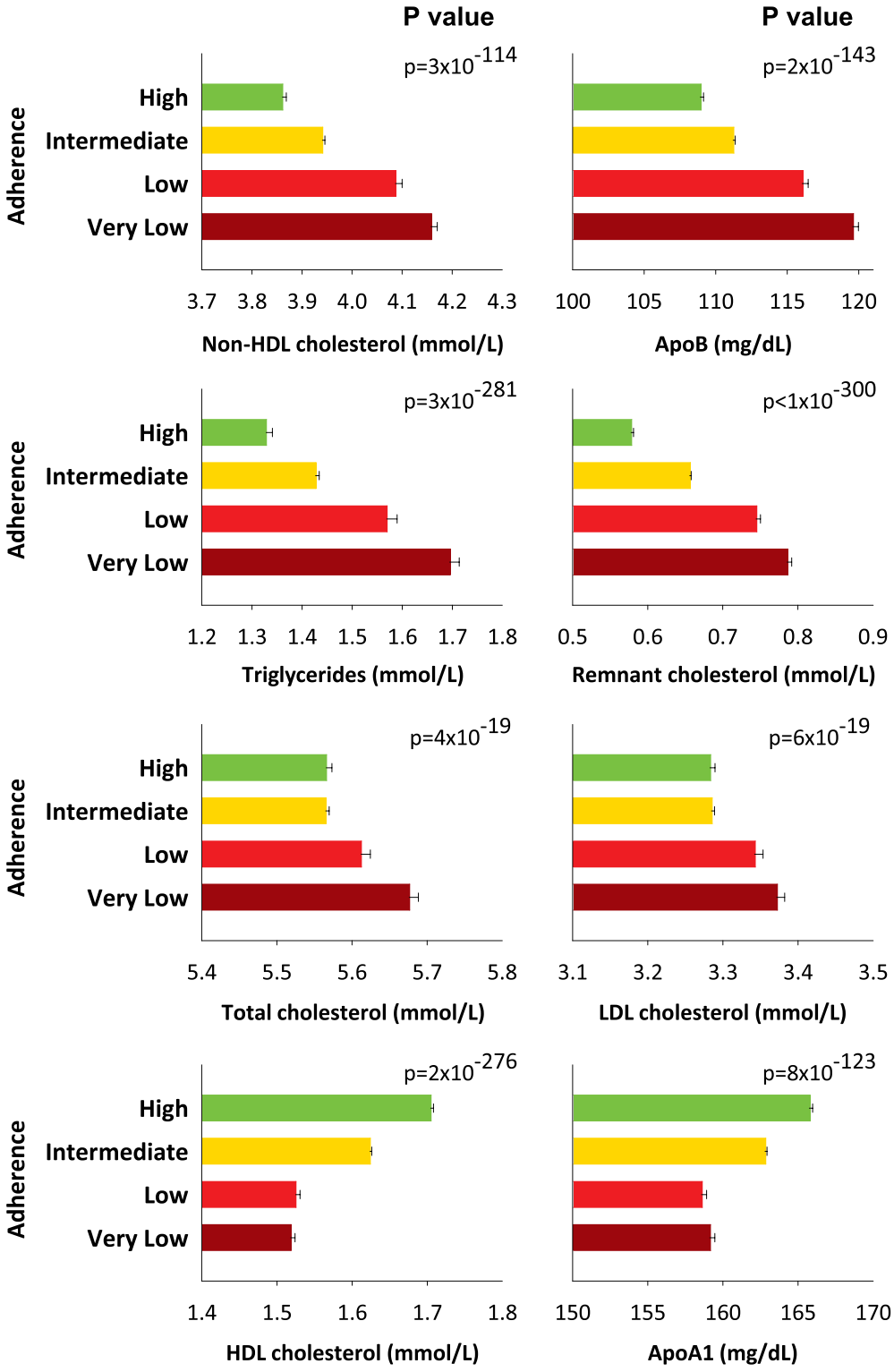

Figure 1. Plasma levels of lipids and lipoproteins according to groups of adherence to dietary guidelines. Arithmetic mean±standard errors of the mean are given for all lipids and lipoproteins except for triglycerides where geometric mean±standard errors of the mean are given. Kruskal-Wallis test was used to calculate p-values. To convert total cholesterol, non-HDL cholesterol, remnant cholesterol, LDL cholesterol, and HDL cholesterol to mg/dL multiply by 38·67. To convert triglycerides to mg/dL multiply by 88·57. ApoA1=apolipoprotein A1; ApoB=a-polipoprotein B; HDL cholesterol= high-density lipoprotein cholesterol; LDL cholesterol=low-density lipoprotein cholesterol.

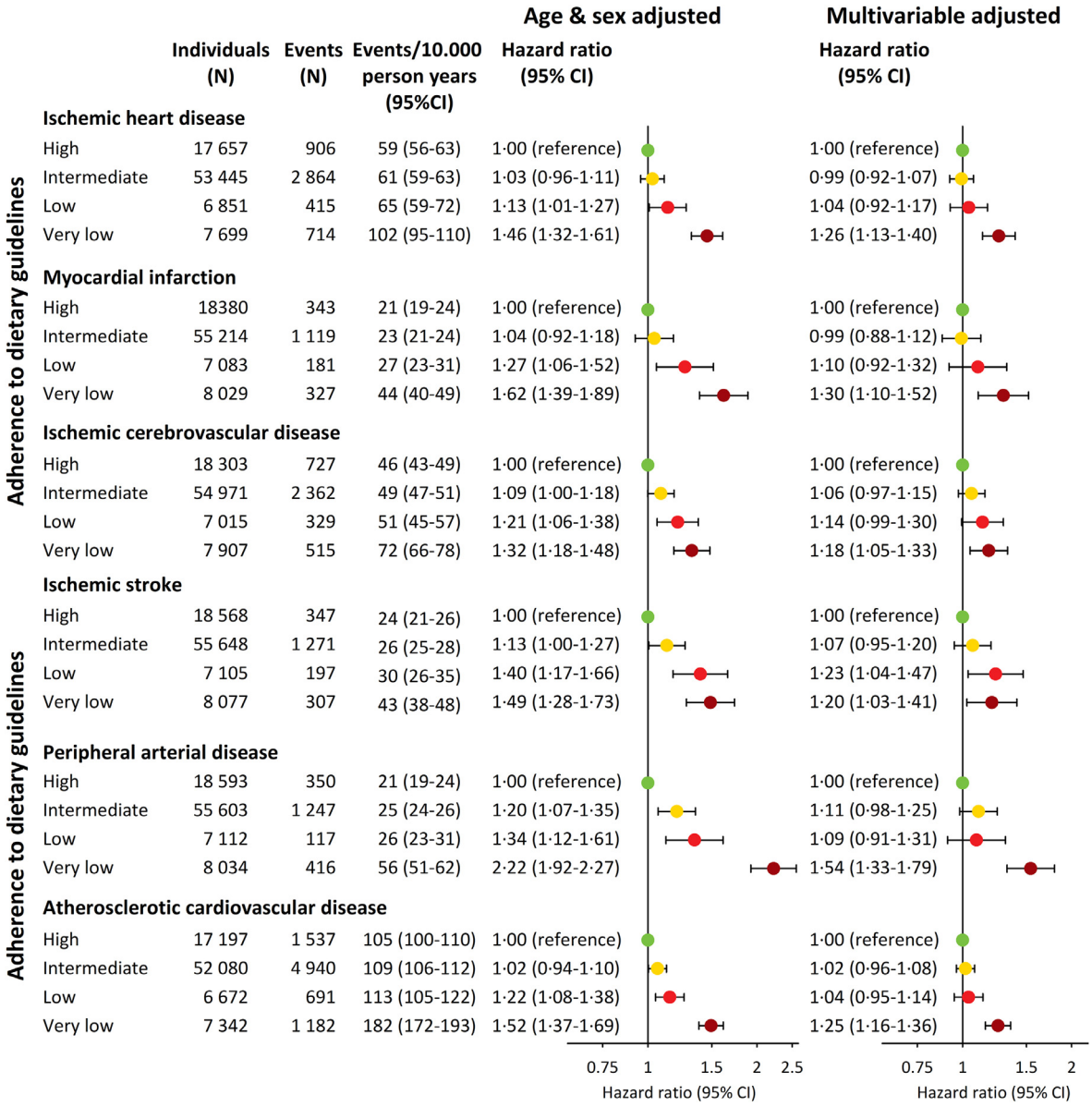

Figure 2. Risk of ASCVD as a function of dietary groups in individuals in the Copenhagen General Population Study. Cox proportional HRs were multivariable adjusted for age (as time scale), sex, household income, educational level, physical activity level, smoking status, alcohol consumption, body mass index, hypertension, lipid lowering therapy, and ischemic heart disease at baseline. ASCVD was defined as the first diagnosis of ischemic heart disease, ischemic cerebrovascular disease, or peripheral arterial disease. ASCVD=atherosclerotic cardiovascular disease; CI=confidence interval.

dietary guidelines, systolic blood pressure between 160 and 179 mmHg, and who were smokers (Figure 4, left chart). Corresponding ten-year absolute risk for women was 26%. Analyses in older individuals (aged 70-89) showed the highest ten-year absolute risk of 45% for men aged 85-89 with very low adherence to dietary guidelines, systolic blood pressure between 160 and 179 mmHg, and who were smokers (Supplementary Figure 8). Corresponding ten-year absolute risk for older women was 36%. Risk charts using non-HDL cholesterol showed similar results as charts including dietary assessment (Figure 4, right chart). Ten-year absolute risk of ASCVD stratified on smoking status increased with increasing age, higher levels of non-HDL cholesterol, and higher systolic blood pressure. The highest ten-year absolute risk of 40% was seen in men aged 65–69 with non-HDL cholesterol between 6·0 and 6·9 mmol/L, systolic blood pressure between 160 and 179 mmHg, and who were smokers. Corresponding ten-year absolute risk for women was 28%.

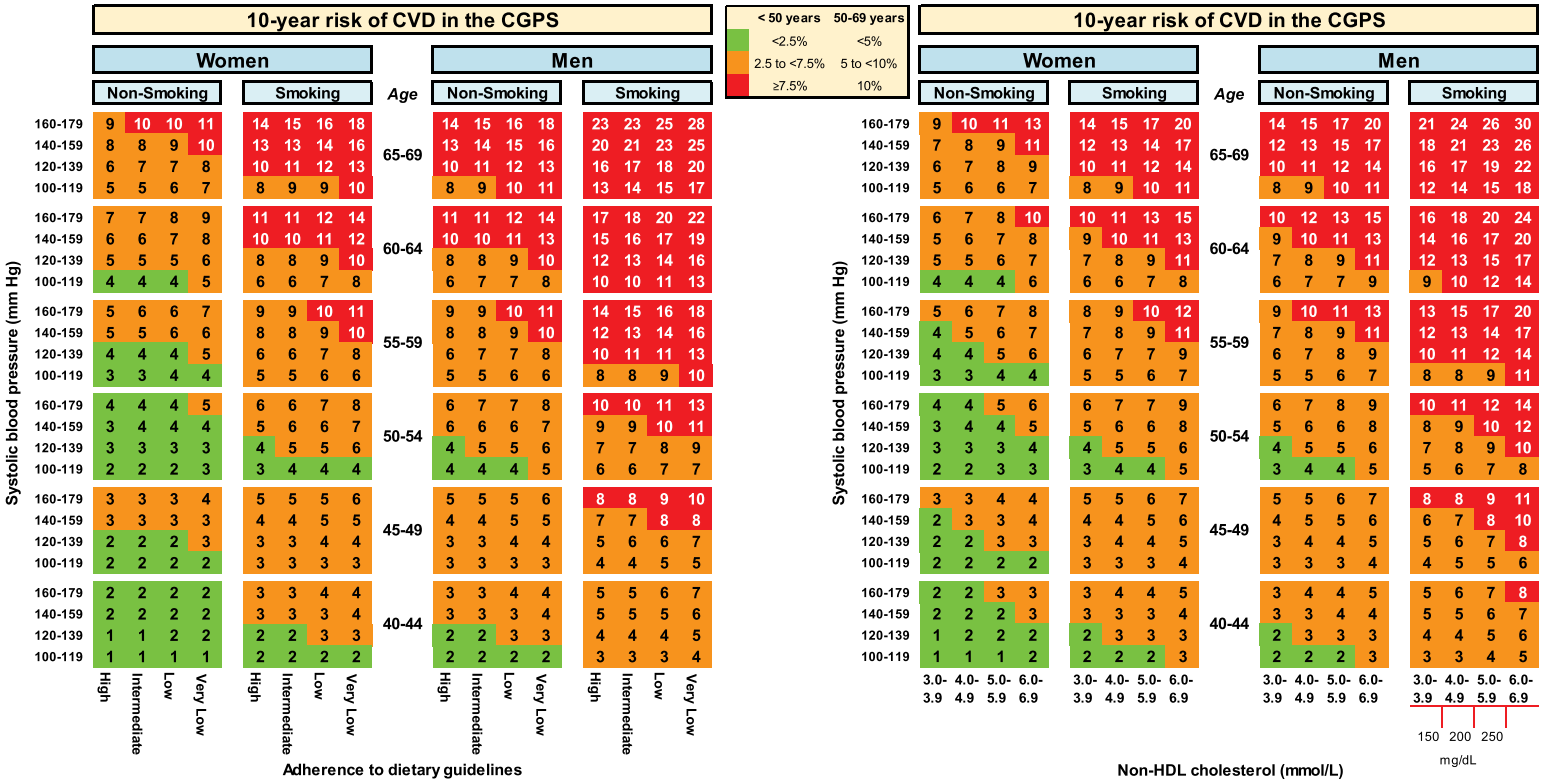

Figure 3. Ten-year risk of CVD based on adherence to dietary guidelines or non-HDL cholesterol levels in the Copenhagen General Population Study. Ten-year absolute risk is determined by identifying sex, smoking status, age-group, systolic blood pressure, and dietary group (left chart) or non-HDL cholesterol level (right chart). CVD included myocardial infarction and stroke. CGPS=Copenhagen General Population Study; CVD=cardiovascular disease; non-HDL cholesterol=non-high-density lipoprotein cholesterol.

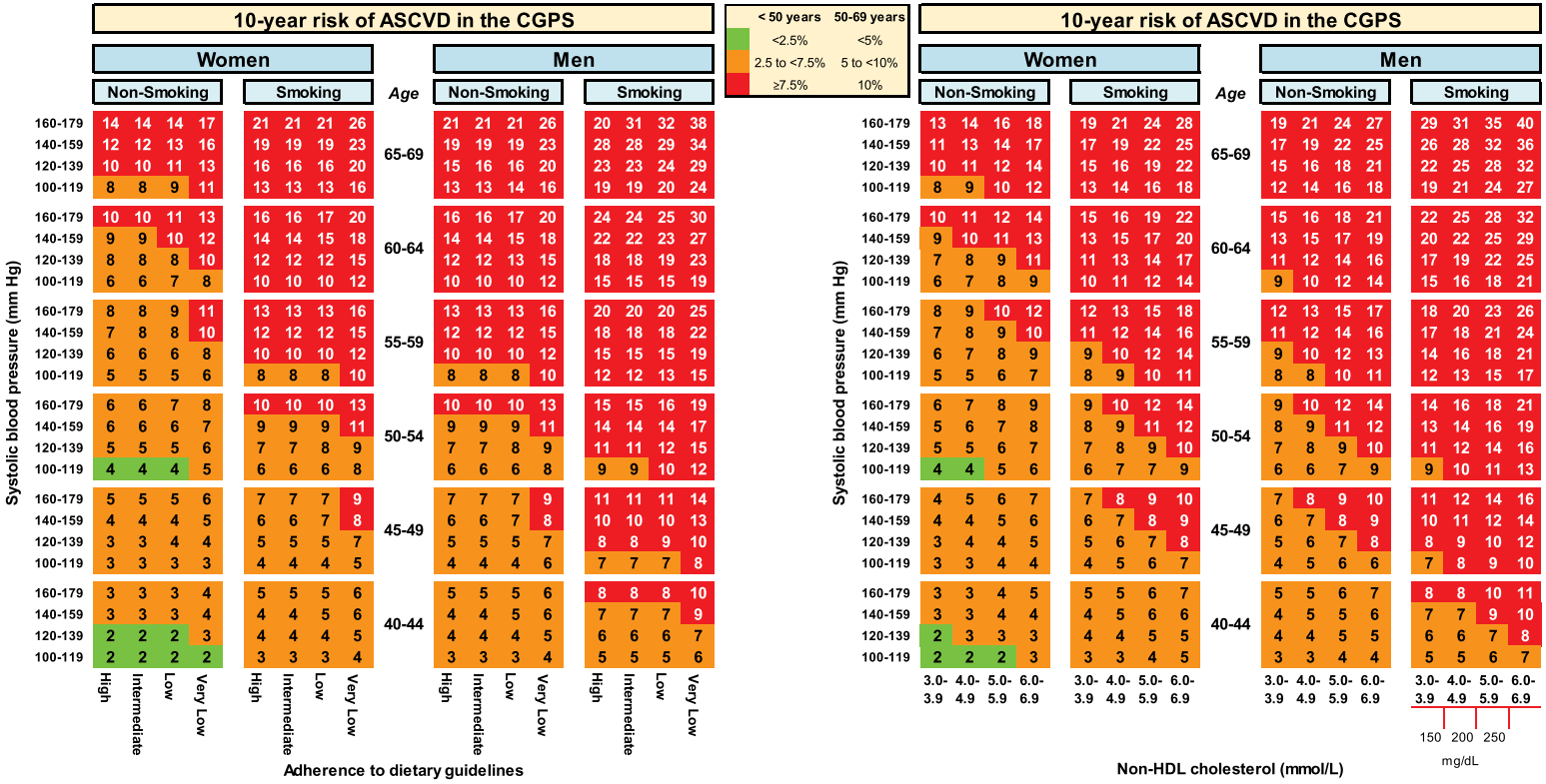

Figure 4. Ten-year risk of ASCVD based on adherence to dietary guidelines or non-HDL cholesterol levels in the Copenhagen General Population Study. Ten-year absolute risk is determined by identifying sex, smoking status, age-group, systolic blood pressure, and dietary group (left chart) or non-HDL cholesterol level (right chart). For example, a 60-year old woman; currently smoking, with low adherence to dietary guidelines, and a systolic blood pressure between 140-159mmHg has a 15% risk of developing ASCVD within the next ten years. ASCVD was defined as the first diagnosis of ischemic heart disease, ischemic cerebrovascular disease, or peripheral arterial disease. ASCVD=atherosclerotic cardiovascular disease; CGPS=Copenhagen General Population Study; non-HDL cholesterol=non-high-density lipoprotein cholesterol.

Analyses in older individuals showed the highest ten-year absolute risk of 44% for men aged 85-89 with non-HDL cholesterol between 5·0 and 5·9 mmol/L, systolic blood pressure between 160 and 179, and who were smokers (Supplementary Figure 8). Corresponding ten-year absolute risk for older women was 34%.

C-indices for the models including dietary assessment and non-HDL cholesterol on risk of ASCVD were 0·675 (0·667-0·683) and 0·665 (0·656-0·673), respectively (Supplementary Table 6). Models were similar in predicting events as the p-value for difference was 0·08. For AUC-ROC the estimate was 0·727 (0·715-0·739) for the diet model and 0·710 (0·698-0·724) for the non-HDL cholesterol model with a p-value for difference in discrimination of 0·06.

Ten-year absolute risk charts for ASCVD including dietary groups in the CCHS showed similar findings as in the CGPS (Supplementary Figure 9). The highest ten-year absolute risk for men of 38% was seen in men aged 65–69 with very low adherence to dietary guidelines, systolic blood pressure between 160 and 179 mmHg, and who were smokers. The corresponding ten-year absolute risk for women was 32%.

Mediated effect of dietary groups on risk of ASCVD

Mediation analysis was performed for ASCVD with non-HDL cholesterol as mediator. The mediated proportion by non-HDL cholesterol for individuals with intermediate, low and very low adherence to dietary guidelines was estimated to 14% (5%-75%), 22% (11%-51%), and 8% (6%-11%), respectively (Supplementary Figure 10). The estimated total, direct and indirect effects are shown in Supplementary Table 7.

Discussion

The principal finding of the present study is that ten-year absolute risk charts for ASCVD showed similar results whether including dietary assessment or non-HDL cholesterol for both men and women (Figure 5). We consider this finding a strong argument in favour of convincing patients to adhere to dietary guideline recommendations. Moreover, we hope that our study can increase the level of evidence for diet recommendations in future guidelines, thus improving public health in general.

Lifestyle management is the first step and first priority in CVD prevention, however, one of the greatest challenges in dietary prevention of CVD is to develop more effective strategies to inspire people to change their diet as well as to maintain it.[6] Looking directly at dietary risk together with your physician may potentially better motivate people to change their dietary habits instead of a blood cholesterol level that for some patients can be difficult to understand. We suggest that charts including dietary risk could be used in general practice or in cardiology departments when estimating a patient's risk of developing CVD or when discussing changing lifestyle habits. Thereby the clinician is supported in providing a targeted prevention strategy that fits patient profile and preferences, as recommended in the 2021 ESC Guidelines on CVD.[6]

Risk estimates in our charts were equivalent to moderate and low CVD risk regions in SCORE2 and SCORE2-OP, respectively.[8,9] The Framingham Risk Score, estimating ten-year cardiovascular risk in a sex-specific algorithm, is another well-known scoring system. It was developed in the United States from a cohort including 8 500 individuals and predicts the risk of coronary heart disease, stroke, peripheral arterial disease, or heart failure based on Cox proportional hazards regression, not taking competing risk of death into account.[25] In the present study, we modelled risk charts based on those of SCORE2 and SCORE2-OP for consistency and comparability measures, as these charts are the most widely used in Europe. The SCORE2 study included 678 000 individuals and predicted risk of fatal and non-fatal cardiovascular events using the method of Fine-Gray.[8] In our study, for the combined ASCVD endpoint, including ischemic heart and ischemic cerebrovascular disease and peripheral arterial disease, we observed substantially higher ten-year absolute risk estimates than for the endpoint of CVD shown in the present paper and used in SCORE2 and SCORE2-OP.[8,9] Interestingly, risk charts for older individuals (70–89 years of age) using dietary assessment appeared to provide higher and more stepwise risk estimates than charts including non-HDL cholesterol. Furthermore, we obsered similar risk discrimination estimates for the models including dietary assessment and for the models including non-HDL cholesterol. Dietary assessment is therefore a strong predictor for absolute risk of CVD in the present ten-year absolute risk charts.

Previous clinical trials and prospective cohort studies report that diet has a relatively large impact on LDL cholesterol concentrations and other apoB containing lipoproteins.[26–32] Substituting dietary intake of saturated fatty acids with unsaturated fatty acids, especially polyunsaturated fatty acids, or with high quality carbohydrates, such as whole grains, reduces total cholesterol, LDL cholesterol levels, and triglyceride levels as a marker for remnant cholesterol.[27,31] In this study, we estimated that non-HDL cholesterol mediated a substantial proportion of the association between diet and ASCVD risk. The well-established causal association between non-HDL cholesterol and ASCVD thus supports the promotion of cholesterol lowering diets.[33] Together, a diet low in saturated fats; low in refined carbohydrates; fairly rich in unsaturated fats, protein (especially plant-based protein e.g. pulses) and high-fibre foods, can reduce LDL cholesterol and triglyceride levels markedly.[9,26,27,30,31] The significance of a diet-induced reduction of atherogenic lipoproteins and ASCVD risk is substantial,[6] supported by this observational study,

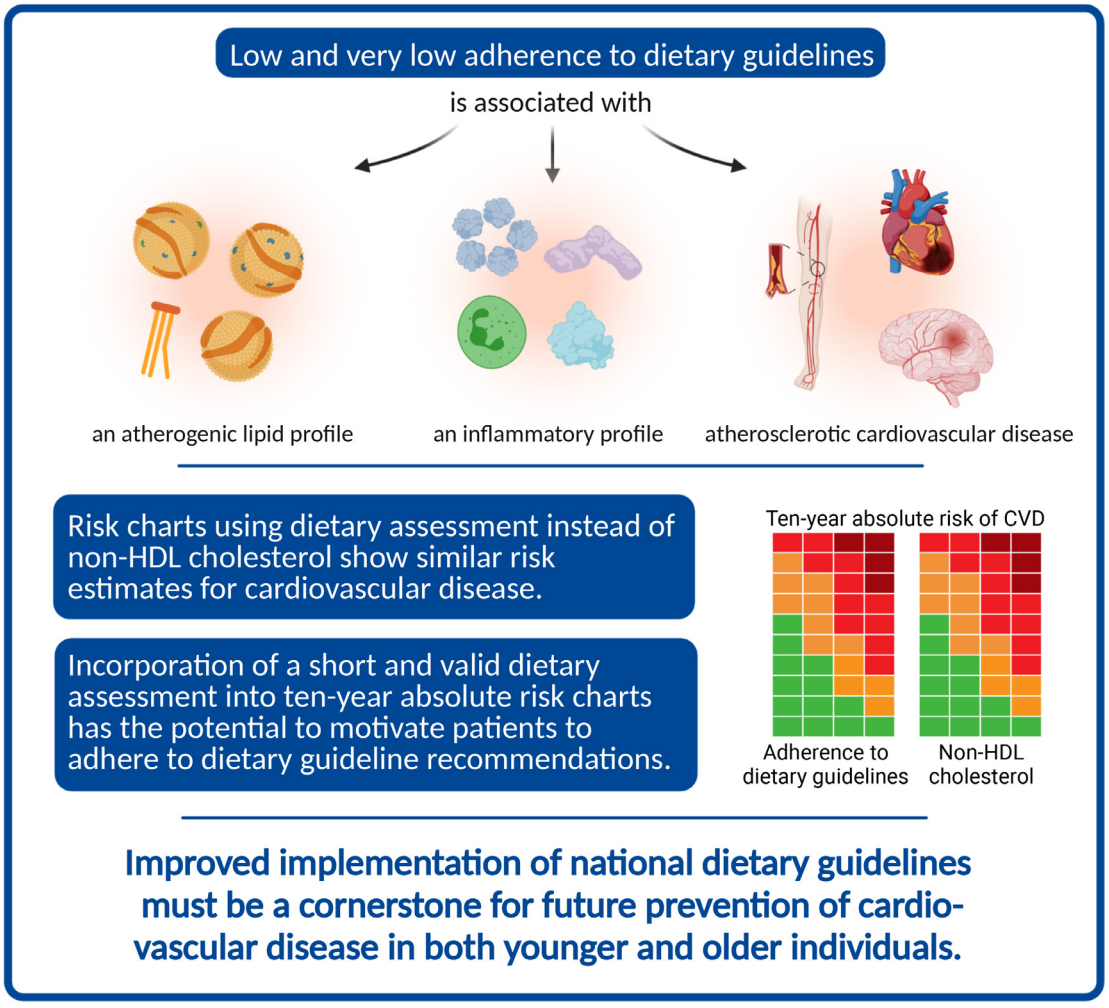

Figure 5. Summarising figure including principal findings and conclusions of a study based on 94 321 individuals in the Danish prospective Copenhagen General Population Study.

emphasizing the importance of effective prevention. Furthermore, unhealthy diets are recognised to be causally associated with increased body mass index and obesity which are important risk factors for hypertension. Moreover, it is well-known that smoking and an unhealthy diet often go together because of a generally unhealthy lifestyle. Thus, by starting healthy interventions in early childhood, these acquired risk factors can be eliminated or remarkedly reduced contributing to so-called primordial prevention – that is preventing risk factors from occuring.[26,34]

This study has several strengths. Firstly, it includes a large sample size of approximately 800 000 person-years of observation representing the general population. Further, we had baseline dietary information and biochemistry measurements preceding the occurrence of an event. Successful event registration for each individual was ensured by the linkage to central registries. Due to the Danish registries we had complete information on death and emigration and not one single individual was lost to follow-up. Detailed information on several confounders at baseline with known associations with ASCVD provided the possibility to include these in multivariable and stratified models as well as in interaction analyses. Results remained significant after exclusion of individuals with less than five years of follow-up, suggesting that reverse causation may not be a major issue. Importantly, we were able to confirm our main findings from the CGPS on ten-year absolute risk in an independent prospective cohort, the Copenhagen City Heart Study (CCHS), where dietary information was available at the fourth visit of the CCHS in 5 385 individuals. Lastly, diets are prone to change over time. We show, however, that more than half of individuals, participating in both baseline and follow-up with complete FFQ data from both visits, remain in the same group of adherence to dietary guidelines while 35% change only one group. Only a minute fraction (<1%)

change dietary habits from high to very low or vice versa. Thus, the presently applied dietary instrument appears robust over time.

Limitations of the current study should be discussed. Dietary assessment was based on self-reported data which may lead to measurement error. Nonetheless, we have previously shown robust associations between diet and all-cause mortality using the present FFQ,[14] indicating that the FFQ serves as a sufficient proxy for dietary habits, and can detect associations between diet and disease. Furthermore, as the exposure is reliant on self-reported data, it is likely that individuals with true low and very low adherence to dietary guidelines report a healthier diet than what is correct leading to fewer individuals exposed. This may cause differential misclassification and would cause a bias towards the null, indicating that the present findings are conservative estimates. Information on macronutrient intake or specific foods were not available, but the simple and few questions included in the FFQ ensured a high response-rate. Our FFQ has not directly been validated, however, a previous Danish study reported that a closely related short FFQ mirrored dietary quality convincingly when compared with an extensive 198 item FFQ.[13] Implementation of extensive FFQs in a clinical setting would be time consuming whereas a short but valid FFQ, describing one's general diet, would be a more realistic tool for the busy clinician and less demanding for the patient. Nonetheless, for this to be realistic to implement in clinical practice, digital solutions should be developed with electronic self-reporting by the patient with direct transfer to the physician's electronic records. Finally, the Copenhagen General Population Study includes whites of Danish descent limiting the applicability of our findings to other nations or ethnicities. Additionally, diets are dependent on countries and even regions, emphasizing the importance of replicating this study in different settings e.g. low and middle-income countries.

In conclusion, incorporating dietary assessment into ten-year absolute risk charts has the potential to convince patients to adhere to dietary guideline recommendations. Improved implementation of national dietary guidelines must be a cornerstone in prevention of CVD, and also has the potential to provide environmental benefits.[4,7,34–37] To achieve Global Sustainable Development Goals 2030 a fundamental transformation of the global food system is needed,[4,34,36,38] and risk charts including dietary assessment can be a tool to change people's diet, not only to a healthier diet, but also to a more sustainable one.

Data availability statement

Danish law does not allow transfer of these data. Upon reasonable request to the corresponding author, the steering committee of the CGPS will evaluate whether data access through direct collaboration can be granted.

Contributors

E.W.K.: Study concept and design, acquisition of data, statistical analysis, analysis and interpretation of data, figures, accessed and verified underlying data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, final approval for submission.

J.Q.T.: Statistical analysis, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, final approval for submission.

K.L.R.: Statistical analysis, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, final approval for submission.

B.G.N.: Acquisition of data, critical revision of the manuscript for important intellectual content, obtained funding, administrative, technical, and material support, final approval for submission.

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Declaration of interests

EWK, JQT, KLR and RFS have nothing to declare. BGN reports consultancies or talks sponsored by AstraZeneca, Sanofi, Regeneron, Akcea, Amgen, Kowa, Denka, Amarin, Novartis, Novo Nordisk, Esperion, and Silence Therapeutics. ATH reports consultancies or talks sponsored by Akcea, AstraZeneca, Draupnir bio, Regeneron, Sanofi, Silence Therapeutics and Novartis.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanepe.2022.100419.

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