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Greater decreases in cholesterol levels among individuals with high cardiovascular risk than among the general population: the northern Sweden MONICA study 1994 to 2014

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Aim Decreasing cholesterol levels in Western populations is the main reason for decreasing mortality due to coronary heart disease. Our aim was to analyze trends in cholesterol levels in the population during a period of 20 years in relation to previous cardiovascular disease (CVD), other cardiovascular risk factors, and socio-economic status.

Methods and results A total of 4546 women and 4349 men aged 25–74 years participated in five population-based surveys in the Northern Sweden MONICA Study between 1994 and 2014 (participation rate 76.8–62.5%). Total cholesterol levels decreased from 6.2 mmol/L (95% confidence interval, CI, 6.1–6.2) in 1994 to 5.5 mmol/L (CI 5.4–5.5) in 2014. The decrease was more pronounced in elderly vs. younger participants (1.0 vs. 0.5 mmol/L). In 2014, participants with previous CVD, diabetes, or hypertension had lower cholesterol levels than the general population, whereas their levels were higher or similar to the general population in 1994. The use of lipid-lowering drugs increased markedly and was used by 14.3% in 2014. Previously described differences in cholesterol levels between participants with obesity and normal weight, and between those with and without university education, diminished, or vanished over time.

Conclusion Cholesterol levels decreased by 0.7 mmol/L over 20 years with no sign of abating. The improvement occurred in all age and gender groups but more prominently among those at high risk of ischaemic heart disease.

Keywords Cholesterol • Lipid-regulating agents • Cardiovascular disease • Diabetes • Obesity • Socioeconomic factors • Epidemiology

Clinical perspective

From 1994 to 2004, total cholesterol levels declined in the population of northern Sweden, especially among individuals with high cardiovascular risk. More intense lipid-lowering drug treatment has contributed to a third of the reduction.

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Introduction

Ischaemic heart disease (IHD) deaths in Sweden have decreased 55–60% due to improved risk factor patterns, mainly lower cholesterol levels.[1] Reduction of total cholesterol by 1 mmol/L is associated with 33% lower IHD mortality among those 50–69 years of age.[2] Analyzing trends in cholesterol levels in the population is important for understanding the dynamics of cardiovascular disease (CVD), especially in groups more vulnerable to high cholesterol levels, i.e. patients with previous CVD or with risk factors. The importance of the total burden of risk factors is the rationale for risk estimation models, such as SCORE used for primary prevention.[3]

In high-income countries in Western Europe, cholesterol levels have decreased 0.2 mmol/L per decade since 1980,[4] although with a slower decrease in the USA.[5] In northern Sweden, cholesterol levels declined 0.9 mmol/L between 1986 and 2009.[6] In the same area, the Västerbotten Intervention Program (VIP) corroborated these findings, but then reported for the first time an increase in cholesterol levels between 2008 and 2010.[7] Diet changes explain most of the early decrease in cholesterol, and statins have probably contributed only recently.[8–11] The introduction of new diets, such as the low-carb high-fat (LCHF) diet, could reverse the beneficial trends towards lower cholesterol levels in the population,[11] overturning the successful primary prevention of IHD.

Our primary aim was to study trends in cholesterol levels between 1994 and 2014 based on five population surveys. Our secondary aim was to analyze these trends in relation to age, sex, prevalent CVD, and its risk factors, and the usage of lipid-lowering agents.

Methods

Survey participants

This study included 25- to 74-year-old participants in the northern Sweden WHO MONICA population-based surveys in 1994, 1999, 2004, 2009, and 2014.[6] In each survey, 2500 participants were randomly selected from population registers stratified for sex and 10-year age groups in the two most northern counties of Sweden. The survey samples were independent of each other. The participant rate declined continuously from 76.8% in 1994 to 62.5% in 2014. Younger men and women have been less prone to participate, and the participation rate remained high among those older than 45 years of age in 2014 (70.3%).[6]

Measurements

Blood samples were drawn after at least a 4-h fast and analyzed without freezing. In 1994, total cholesterol was determined by an enzymatic method (BM Monotest Cholesterol CHOD-PAP, Boehringer Mannheim GmbH, Germany), and since 1999 a dry chemistry method was used (Vitros 950, Kodak Echtachem, USA).[9] The measurement of total cholesterol is accredited by the national accreditation body, with a CV of 3.6% at 3.9 mmol/L and 3.1% at 6.7 mmol/L. We defined a desirable cholesterol level in the population without CVD, diabetes, or hypertension as <5.0 mmol/L.[3]

Blood pressure was measured twice in a sitting position after a 5-min rest and the mean value recorded. Hypertension was defined as a mean systolic blood pressure ≥ 140 mmHg and/or mean diastolic blood pressure ≥ 90 mmHg and/or reported use of antihypertensive medication. Diabetes and previous myocardial infarction or stroke was self-reported. The highest attained education was used as a proxy for socioeconomic status and dichotomized into university education (yes/no). Participants who smoked at least one cigarette a day were classified as regular smokers. Anthropometric measurements were performed by specially trained nurses using the same standardized methods in all surveys.[6]

Statistical methods

Sex- and age-specific mean total cholesterol levels and the proportions of participants using lipid-lowering drugs were presented with 95% confidence intervals (CIs) based on a normal approximation. The change in mean levels from 1994 to 2014 was calculated using separate general linear models for each sex and age strata assuming a linear trend over time. To test for age group differences in the trend, an additional model included all strata and the factors age group, sex, year of survey, and all corresponding two-way interactions.

Age-adjusted cholesterol levels in subgroups of patients based on self-reported diabetes (yes/no), hypertension (above/below 140/90 mmHg with or without medication), BMI (<25, >30), previous stroke or myocardial infarction (yes/no), and university education (yes/no) were analyzed by general linear models and presented as estimated marginal means at the mean age of 51 years unless otherwise stated. Age was included as a continuous covariate in addition to the categorical factors sex, year of screening, subgroup, sex*subgroup, year*subgroup, sex*year, and sex*year*subgroup. The proportion of participants using lipid-lowering drugs was analyzed in a similar way using a generalized linear model assuming a Poisson distribution and log link. Data were analyzed as if generated from simple random sample. *P*-value of <0.05 was considered significant. IBM SPSS statistics 22.1 was used for statistical analyses.

Ethical considerations

This study complies with the Declaration of Helsinki and was approved by the ethical review board in Umeå. Informed consent was obtained from all participants.

Results

A total of 8941 men and women participated in the five surveys between 1994 and 2014. Cholesterol values were missing for 46 participants, resulting in 4546 women and 4349 men being included in the study.

Overall, the observed mean cholesterol levels decreased approximately linearly from 6.2 mmol/L (CI 6.1–6.2) in 1994 to 5.5 mmol/L (CI 5.4–5.5) in 2014. The levels decreased among both women and men and in all age groups ($P < 0.001$ for all groups; *Figure 1* and Supplementary material online, *Table S1*). Assuming a linear trend, the estimated absolute decline in cholesterol levels in the oldest age group (65–74 years) was 1.1 mmol/L (CI 0.9–1.3) in women and 1.0 mmol/L (CI 0.8–1.2) in men. The corresponding decline was lower in younger age groups (year-by-age group interaction $P < 0.001$), with a 0.5 mmol/L (CI 0.4–0.7) decline in women and 0.6 mmol/L (CI 0.3–0.8) decline in men in the youngest age group (25–34 years). As the cholesterol levels in 1994 were higher in the oldest age group, the difference in relative change across age groups was small.

In 2014, 73.2% (CI 64.9–81.5) of all women and 64.1% (CI 54.7–73.5) of all men in the 25–34 years age group had cholesterol levels

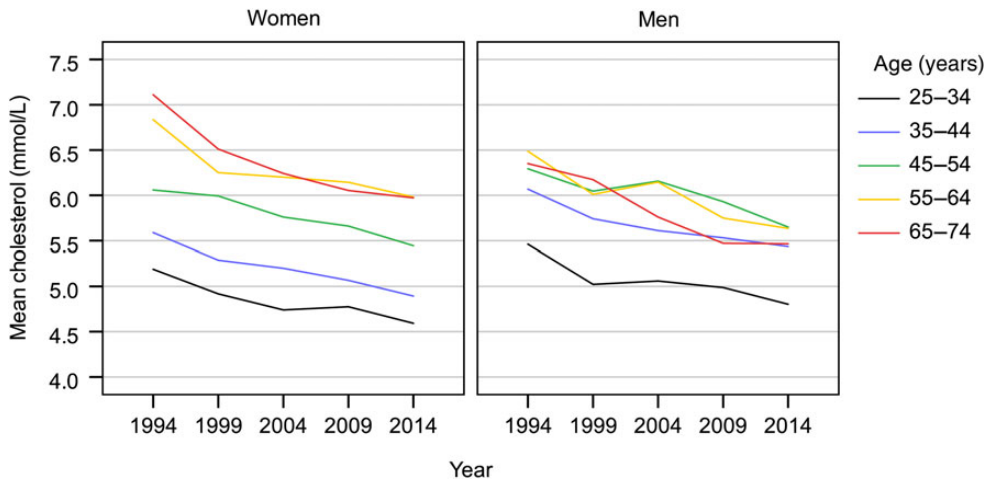

Figure 1 Mean total cholesterol levels (mmol/L) in men and women based on 10-year age groups.

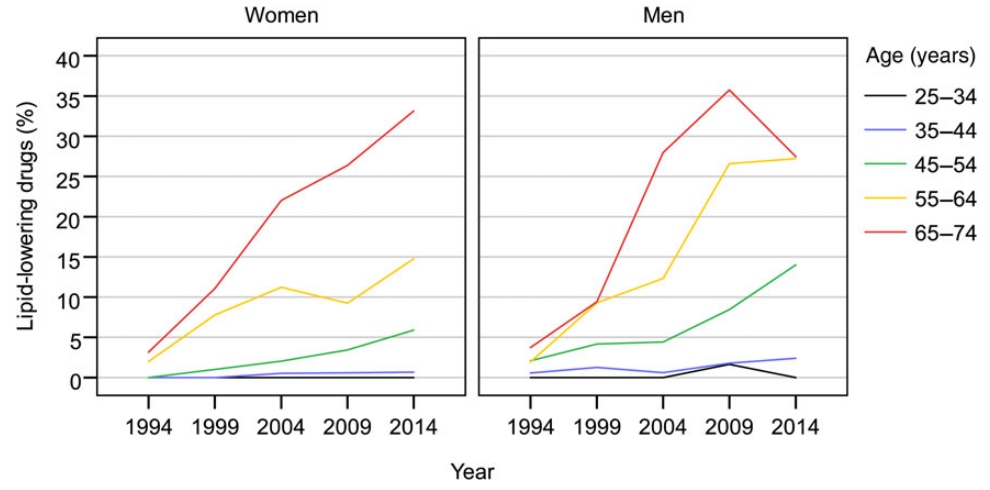

Figure 2 Proportion (%) of men and women taking lipid-lowering drugs based on 10-year age groups.

<5.0 mmol/L (Supplementary material online, *Figure S1*). The proportion decreased markedly with higher age, especially in women, reaching its lowest level in 55- to 64-year-old women (14.4%, CI 9.3–19.6).

In the participants without diabetes, history of stroke, or myocardial infarction, the proportion with cholesterol levels <5.0 mmol/L increased from 19.5% (CI 17.0–22.0) in 1994 to 36.6% (CI 33.3–40.0) in 2014 among women and from 17.8% (CI 15.3–20.2) to 36.7% (CI 33.3–40.2) among men.

Between 1994 and 2014, the observed use of lipid-lowering drugs in the population increased from 1.4% (CI 0.8–1.9) to 14.3% (CI 12.6–16.1). In 2014, 33.1% (CI 26.2–40.1) of women and 27.5% (CI 20.9–34.0) of men in the oldest age group (65–74 years) were using lipid-lowering drugs (*Figure 2*).

In clinical praxis, statin treatment is expected to lower the total cholesterol level by an average of 1.5 mmol/L or ~30%.[8–10] We used 1.5 mmol/L to calculate the hypothetical cholesterol levels in a population with no medication in 2014: 5.6 mmol/L in women and 5.7 mmol/L in men (actual levels 5.5 and 5.4 mmol/L, respectively). In the oldest age group (65–74 years), which used lipid-lowering drugs most frequently, the difference was 6.5 vs. 6.0 mmol/L in women and 5.9 vs. 5.5 mmol/L in men. A crude estimate[8] (proportion with drugs × effect of drugs in clinical praxis/estimated reduction in cholesterol level) suggested that lipid-lowering drugs accounted for ≈31% of the reduced cholesterol levels between 1994 and 2014 in the 25–74 years age group, and ≈44% in the oldest age group (65–74 years).

Diabetes

The prevalence of self-reported diabetes increased from 3.1% (CI 2.4–3.9) in 1994 to 4.9% (CI 3.8–6.0) in 2014 ($P = 0.003$, test for linear trend). Initially, cholesterol levels were similar in participants

with and without diabetes, though the level declined faster among those with diabetes (decline between 1994 and 2014: 1.6 mmol/L, CI 1.0–2.1 vs. 0.9 mmol/L, CI 0.8–1.1; year-by-diabetes interaction $P < 0.001$, *Figure 3*).

The observed use of lipid-lowering drugs in diabetic patients increased from 10.2% (CI 2.2–18.1) in 1994 to 59.7% (CI 48.1–71.3) in 2014, which is considerably higher than in non-diabetic participants ($P < 0.001$). No difference was found between men and women with diabetes in regards to the use of lipid-lowering drugs.

Hypertension

Hypertension was less common among women than men (35.9%, CI 34.5–37.3 vs. 45.5%, CI 44.0–47.0), with no clear time trend. In 2014, the participants who achieved normal blood pressure levels with antihypertensive treatment had the lowest age-adjusted cholesterol levels (5.5 mmol/L, CI 5.4–5.6), followed by participants with high blood pressure despite antihypertensive treatment (5.7 mmol/L, CI 5.6–5.8), participants with normal levels and no antihypertensive treatment (5.7 mmol/L, CI 5.7–5.8), and participants with high blood pressure levels and no antihypertensive treatment (6.0 mmol/L, CI 5.9–6.1; *Figure 4*).

In participants with hypertension, the use of lipid-lowering drugs increased from 2.8% (CI 1.6–4.0) in 1994 to 27.6% (CI 24.0–31.0) in 2014. The age-adjusted proportion of participants using lipid-lowering drugs in 2014 (adjusted to the mean age of hypertensive participants, 59 years) was higher among hypertensive participants than among those with normal blood pressure levels and no antihypertensive treatment (20.3%, CI 17.3–23.9 vs. 8.6%, CI 6.5–11.4).

Obesity

The prevalence of obesity (BMI > 30) increased from 14.6% (CI 13.0–16.2) in 1994 to 22.4% (CI 20.4–24.5) in 2014. In 1994, obese participants had higher cholesterol than normal-weight participants (BMI < 25), but this difference diminished over time (Supplementary material online, *Figure S2*). In 2014, obese participants had even lower cholesterol levels than non-obese participants (BMI ≤ 30) in the two oldest age groups (>54 years).

Among obese participants, the observed use of lipid-lowering drugs increased from 1.1% (CI 0–2.3) in 1994 to 21.2% (CI 16.9–25.6) in 2014. In 2014, the difference in lipid-lowering drug use between obese and non-obese participants was pronounced in the 55–64 years age group (34.1%, CI 24.0–44.2 vs. 16.4%, CI 11.8–21.0) but not significant in other age groups.

Smoking

The prevalence of smokers decreased from 21.0% (CI 19.1–22.8) in 1994 to 7.7% (CI 6.4–9.0) in 2014. The difference in cholesterol levels between smokers and non-smokers was small throughout the study period (Supplementary material online, *Figure S3*) and did not differ in 2014. The proportion of participants using lipid-lowering drugs did not differ between smokers and non-smokers.

History of myocardial infarction or stroke

The prevalence of previous CVD was 4.9% (CI 4.4–5.4) and did not change during the period. The estimated mean cholesterol levels (adjusted to mean age of participants with CVD, 64 years) did not differ between participants with and without a history of CVD in 1994. In the intervening years, cholesterol levels declined faster in men and women with CVD than those without ($P < 0.001$, *Figure 5*). In 2014, the estimated levels reached 4.9 mmol/L (CI 4.6–5.2) in participants with CVD compared with 5.9 mmol/L (CI 5.8–6.0) in participants without a history of CVD. In parallel, the use of lipid-lowering drugs increased faster in participants with a history of CVD ($P < 0.001$), reaching 49.9% (CI 35.8–69.5) in 2014, compared with 20.0% (CI 17.2–23.2) in participants without CVD (age adjusted to 64 years).

Education

The proportion of participants with university education increased from 17.9% (CI 16.2–19.6) in 1994 to 32.7% (CI 30.4–35.1) in 2014. Cholesterol levels were similar in men with and without university education throughout the study period. In 1994, women without

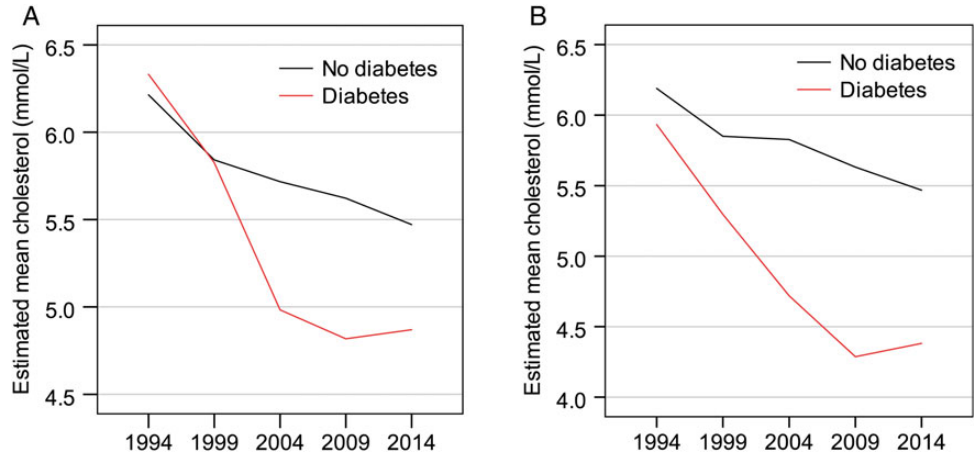

Figure 3 Estimated mean total cholesterol levels (mmol/L) among participants with or without known diabetes. (*A*) Women, (*B*) men.

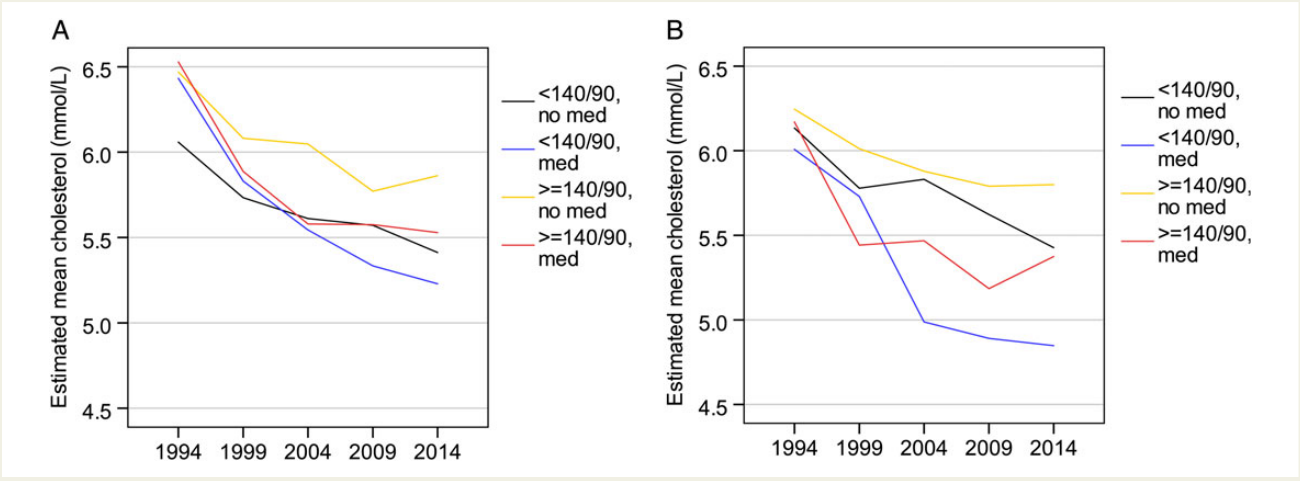

Figure 4 Estimated mean total cholesterol levels (mmol/L) among participants with or without hypertension and antihypertensive medication. (*A*) Women, (*B*) men.

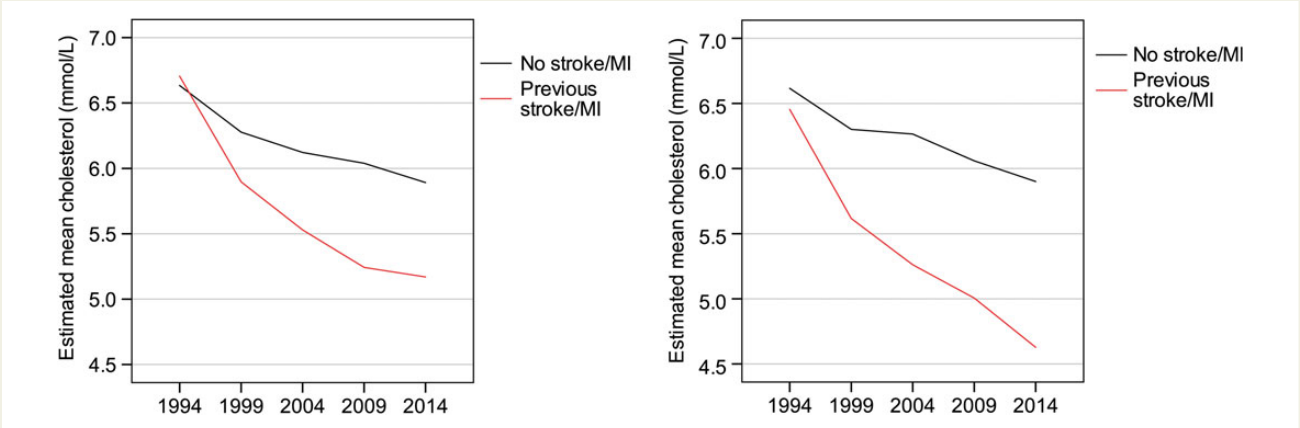

Figure 5 Estimated mean total cholesterol levels (mmol/L) among participants with or without previous stroke or myocardial infarction. (*A*) Women, (*B*) men.

university education had on average 0.5 mmol/L higher cholesterol levels than women with university education ($P < 0.001$). However, cholesterol levels improved faster in women with non-university levels, and the difference was no longer apparent in 2014 (Supplementary material online, *Figure S4*). Treatment with lipid-lowering drugs did not differ between participants with and without university education.

Discussion

From 1994 to 2014, total cholesterol levels continuously decreased among the population of Northern Sweden in all age and gender groups. More pronounced improvement in cholesterol was evident in groups with an increased risk of CVD and in women with lower education. In 2014, treatment with lipid-lowering drugs contributed modestly to lower cholesterol levels, but among the oldest age group such treatment was estimated to decrease cholesterol by 0.5 mmol/L. The more extensive use of lipid-lowering drugs in participants with diabetes and CVD may explain most of the greater decline in cholesterol levels.

Cholesterol levels are decreasing in the Western world, though no studies have included data beyond 2010.[4,6,7,10] In Northern Sweden, cholesterol levels decreased by 0.3 mmol/L per decade, more than the 0.2 mmol/L per decade reported in the meta-analysis by the Global Burden of Disease group.[4]

Changes in diet have been the major driving force in northern Sweden in the MONICA and VIP studies,[11] with decreasing intake of both total fat and saturated fat up to 2004. During 2008–2010, the trend of decreasing cholesterol levels in the VIP study was reversed[7] and a causal link between changes in diet and levels of cholesterol seemed feasible. The widespread introduction of the LCHF diet was suggested to influence the mean levels in the whole

population.[11] However, a recent update from the VIP study[12] described decreasing values. Therefore, it is likely that the LCHF diet peaked before 2014 and a transient effect on cholesterol levels was not detected by the MONICA study sampling only in 2009 and 2014. Within the MONICA study diet patterns have been compared in 1986 and 2004[13] and a decrease in intake of all types of fat was observed. Furthermore, there was an increase in intake of fiber from fruits, vegetables, and grains. Thus, improvements in diet probably contributed to the decrease in cholesterol.

Cholesterol levels decreased in both men and women and in all age groups to a similar (relative) extent, though the absolute decrease was markedly greater among the oldest age group, in which the use of statins strongly contributed. This finding is in accordance with our previous report extending back to 1986.[9]

Half of the improvement in cholesterol levels in the UK and almost all of the improvement in the USA is due to statins.[8] In 2008, the effect of statins on population levels in Iceland was estimated to be 1–2%,[10] in line with the 2% we reported from northern Sweden in 2004[9] and lower than the 31% in this report. Among the elderly, the effect was even greater, 44% in 2014, which is also much higher than the reported 6% in Iceland in 2008.[10] The important public health message from this study is that, even after many years of decreasing cholesterol levels, there are still possibilities for further improvement by diet modifications, and statin treatment in selected groups.[1]

Although a high cholesterol level is an independent cardiovascular risk factor, the risk at any given level depends on the occurrence or level of other risk factors. Therefore, CVD risk estimation models, such as SCORE,[3] also take into account age, sex, systolic blood pressure, and smoking. For an effective high-risk strategy for the prevention of CVD, the cholesterol levels and trends among individuals with other cardiovascular risk factors are important but seldom reported.

For patients with diabetes, specific risk prediction models have been constructed from national cohorts of diabetes patients,[14] which give cholesterol levels a central role. The causal link between lower cholesterol levels due to statin treatment and less CVD in diabetic patients was finally settled in 2002,[15] leading many guidelines to propose statins to all patients with type 2 diabetes. In Northern Sweden, 60% of all patients with diabetes are now treated with statins resulting in almost 1 mmol/L lower cholesterol than in the non-diabetic population. Together with lower blood pressure, this is probably the most important explanation for better survival among Swedish diabetics with myocardial infarction.[16]

Treatment of hypertension reduces the risk of CVD by 25–30%, whereas adding statins can further reduce the risk by 35–40%.[17,18] In the USA, concomitant control of both hypertension and hypercholesterolemia has improved since 1988, but in 2010 only one-third of the hypertensive population adequately controlled both risk factors.[17] Hypertensive participants with adequate blood pressure control in this study had the lowest cholesterol levels, and levels declined faster among drug-treated hypertensives, lending support to the quality of primary health care in Sweden. However, we also noted remove the highest cholesterol levels among participants with high blood pressure without treatment, a group with very high predicted CVD risk. Identifying these individuals should be of the utmost importance.

Whether being overweight and obese is associated with higher mortality is being debated.[19] The disagreement may be due to the fact that the prevalence of 'metabolic health' among obese persons has increased.[20] We previously reported higher total cholesterol levels in obese participants.[9] This difference was not observed when we extended the observation to 2014, which was explained to a large extent by statins being prescribed to one-third of middle-aged obese participants.

We did not find any difference in cholesterol levels between smokers and non-smokers. However, this could be misleading as HDL was not measured and a smoking-induced HDL reduction with a more detrimental HDL/LDL ratio could not be detected.[21]

The importance of lowering cholesterol levels after a myocardial infarction is highlighted in contemporary treatment guidelines.[3] Despite this, many patients with known coronary heart disease (CHD) still have elevated cholesterol levels.[22] The proportion of Swedish patients with LDL <2.5 mmol/L 1 year after a coronary event increased only marginally between 2005 and 2012,[23] probably due to low adherence to statins. In 2009, only 56% of patients with ischaemic stroke remained on statins 2 years after the event.[24] We found a much faster decrease in cholesterol levels in patients with stroke and/or myocardial infarction than in the general population. A 1.6 mmol/L decrease in cholesterol levels among CHD patients between 1986 and 2002 prevented 1350 deaths.[1]

Low education is a strong predictor of IHD,[25] and its inclusion in SCORE improved the accuracy of risk estimation,[26] partly due to higher cholesterol levels among people with low education.[9] In the USA, the disparity gap in cholesterol was stable.[27] Recent studies from Scandinavia have presented data up to 2010 and found stable[28] or diminishing[7,29] educational inequalities in cholesterol levels as well as a levelling off.[30] We found no differences according to education among men, and the higher cholesterol initially noted among women with low education were not present in 2014. This is encouraging and supports the joint efforts of society and health care in achieving a healthier life style and that they have also reached deprived groups.

It was previously estimated that declining cholesterol by 1 mmol/l would lead to 23% lower CVD mortality.[2] According to the Swedish cause of death register, CVD mortality did decrease by 49% from 1997 to 2014 in the 25–74 age span in the region. A modelling study from Sweden supports that declining population levels of cholesterol levels explain half of the reduction in CVD mortality.[1]

A possible limitation is the change of laboratory methods or a drift in measurements over time. However, the assays used have been carefully quality assured by the national accreditation body throughout the survey period. The change in methods between 1994 and 1999 led to 1.4% higher values, and previous measurements have been corrected accordingly. Decreasing attendance, especially among the youngest age group, is a possible problem, but as the youngest age group had the lowest cholesterol levels, the true level in the population may even be lower than that reported in this study. The change in mean cholesterol levels from 1994to 2014 was estimated assuming a linear trend, and this estimate may be biased if the linearity assumption is violated. However, the estimated change was similar to the observed difference comparing the surveys 1994 and 2014, suggesting no major bias. The strength of this study is the repeated measurements with standardized and quality controlled

methods in a very stable population within a well-defined geographical area. Although total cholesterol levels have shown good predictive value in epidemiological studies, it is advisable in the individual patient also to evaluate other lipoproteins such as LDL and HDL, which we have not measured in MONICA.

Conclusion

Total cholesterol levels in the population of northern Sweden have declined 0.7 mmol/L over 20 years. The improvement occurred in all age and gender groups, but more prominently in those at high cardiovascular risk and in women with low education. More intense lipid-lowering drug treatment was estimated to contribute to a third of the reduction. However, there were still high-risk participants with non-satisfactory cholesterol levels without lipid-lowering drugs. This study underscores the importance of surveillance of cardiovascular risk factors in the population, as improvements are the most effective way to combat CVD.

Authors' contributions

M.Er. performed statistical analysis. M.El., S.S. handled funding and supervision. All authors: acquired the data. M.Er., M.El., J.-H.J. conceived and designed the research. M.Er., M.El., drafted the manuscript. All authors made critical revision of the manuscript for key intellectual content

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Conflict of interest: none declared.

References

1. Björck L, Capewell S, O'Flaherty M, Lappas G, Bennett K, Rosengren A. Decline in coronary mortality in Sweden between 1986 and 2002: comparing contributions from primary and secondary prevention. *PLoS ONE* 2015;**10**:e0124769.
2. Prospective Studies Collaboration, Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R, Collins R. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet* 2007;**370**:1829–1839.
3. Fifth Joint Task Force of the European Society of Cardiology, European Association of Echocardiography, European Association of Percutaneous Cardiovascular Interventions, European Heart Rhythm Association, Heart Failure Association, European Association for Cardiovascular Prevention & Rehabilitation, European Atherosclerosis Society, International Society of Behavioural Medicine, European Stroke Organisation, European Society of Hypertension, European Association for the Study of Diabetes, European Society of General Practice/Family Medicine, International Diabetes Federation Europe, European Heart Network. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur J Prev Cardiol* 2012;**19**:585–667.
4. Farzadfar F, Finucane MM, Danaei G, Pelizzari PM, Cowan MJ, Paciorek CJ, Singh GM, Lin JK, Stevens GA, Riley LM, Ezzati M, Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Cholesterol). National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3.0 million participants. *Lancet* 2011;**377**:578–586.
5. Carroll MD, Kit BK, Lacher DA, Shero ST, Mussolino ME. Trends in lipids and lipoproteins in US adults, 1988–2010. *J Am Med Assoc* 2012;**308**:1545–1554.
6. Eriksson M, Holmgren L, Janlert U, Jansson JH, Lundblad D, Stegmayr B, Soderberg S, Eliasson M. Large improvements in major cardiovascular risk factors in the population of northern Sweden: the MONICA study 1986–2009. *J Intern Med* 2011;**269**:219–231.
7. Ng N, Johnson O, Lindahl B, Norberg M. A reversal of decreasing trends in population cholesterol levels in Vasterbotten County, Sweden. *Glob Health Action* 2012; **5**: doi: 10.3402/gha.v5i0.10367.
8. Capewell S, Ford E. Why have total cholesterol levels declined in most developed countries? *BMC Public Health* 2011;**11**:641.
9. Eliasson M, Janlert U, Jansson JH, Stegmayr B. Time trends in population cholesterol levels 1986–2004: influence of lipid-lowering drugs, obesity, smoking and educational level. The northern Sweden MONICA study. *J Intern Med* 2006;**260**:551–559.
10. Thorsson B, Steingrimsdottir L, Halldorsdottir S, Andersen K, Sigurdsson G, Aspelund T, Gudnason V. Changes in total cholesterol levels in Western societies are not related to statin, but rather dietary factors: the example of the Icelandic population. *Eur Heart J* 2013;**34**:1778–1782.
11. Johansson I, Nilsson LM, Stegmayr B, Boman K, Hallmans G, Winkvist A. Associations among 25-year trends in diet, cholesterol and BMI from 140,000 observations in men and women in Northern Sweden. *Nutr J* 2012;**11**:40-2891-11-40.
12. Lönnberg G. VIP 1990-2014. **http://public.tableau.com/views/VHU1990-2014/Kolesterol?:embed=y&:toolbar=no&:loadOrderID=0&:display_count=yes&:showTabs=y (14 July 2015)**.
13. Krachler B, Eliasson M, Stenlund H, Johansson I, Hallmans G, Lindahl B. Population-wide changes in reported lifestyle are associated with redistribution of adipose tissue. *Scand J Public Health* 2009;**37**:545–553.
14. Zethelius B, Eliasson B, Eeg-Olofsson K, Svensson AM, Gudbjornsdottir S, Cederholm J, NDR. A new model for 5-year risk of cardiovascular disease in type 2 diabetes, from the Swedish National Diabetes Register (NDR). *Diabetes Res Clin Pract* 2011;**93**:276–284.
15. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7–22.
16. Eliasson M, Jansson JH, Lundblad D, Näslund U. The disparity between long-term survival in patients with and without diabetes following a first myocardial infarction did not change between 1989 and 2006: an analysis of 6,776 patients in the Northern Sweden MONICA Study. *Diabetologia* 2011;**54**:2538–2543.
17. Egan BM, Li J, Qanungo S, Wolfman TE. Blood pressure and cholesterol control in hypertensive hypercholesterolemic patients: national health and nutrition examination surveys 1988–2010. *Circulation* 2013;**128**:29–41.
18. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J, ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;**361**:1149–1158.
19. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA* 2013;**309**:71–82.
20. Benckert M, Lilja M, Söderberg S, Eliasson M. Improved metabolic health among the obese in six population surveys 1986 to 2009: the Northern Sweden MONICA study. *BMC Obesity* 2015;**2**:7.
21. Forey BA, Fry JS, Lee PN, Thornton AJ, Coombs KJ. The effect of quitting smoking on HDL-cholesterol - a review based on within-subject changes. *Biomark Res* 2013; **1**:26-7771-1-26.
22. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyörälä K, Keil U, EUROASPIRE Study Group. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. *Lancet* 2009;**373**:929–940.
23. Hambraeus K, Tyden P, Lindahl B. Time trends and gender differences in prevention guideline adherence and outcome after myocardial infarction: data from the SWEDEHEART registry. *Eur J Prev Cardiol* 2016;**23**:340–348.
24. Glader EL, Sjölander M, Eriksson M, Lundberg M. Persistent use of secondary preventive drugs declines rapidly during the first 2 years after stroke. *Stroke* 2010;**41**: 397–401.
25. Rosengren A, Subramanian SV, Islam S, Chow CK, Avezum A, Kazmi K, Sliwa K, Zubaid M, Rangarajan S, Yusuf S, INTERHEART Investigators. Education and risk for acute myocardial infarction in 52 high, middle and low-income countries: INTERHEART case-control study. *Heart* 2009;**95**:2014–2022.
26. Ferrario MM, Veronesi G, Chambless LE, Tunstall-Pedoe H, Kuulasmaa K, Salomaa V, Borglykke A, Hart N, Soderberg S, Cesana G, MORGAM Project. The contribution of educational class in improving accuracy of cardiovascular risk prediction across European regions: the MORGAM Project Cohort Component. *Heart* 2014;**100**:1179–1187.

27. Kanjilal S, Gregg EW, Cheng YJ, Zhang P, Nelson DE, Mensah G, Beckles GL. Socioeconomic status and trends in disparities in 4 major risk factors for cardiovascular disease among US adults, 1971–2002. *Arch Intern Med* 2006;**166**: 2348–2355.
28. Ernstsen L, Strand BH, Nilsen SM, Espnes GA, Krokstad S. Trends in absolute and relative educational inequalities in four modifiable ischaemic heart disease risk factors: repeated cross-sectional surveys from the Nord-Trondelag Health Study (HUNT) 1984–2008. *BMC Public Health* 2012;**12**:266-2458-12-266.
29. Eggen AE, Mathiesen EB, Wilsgaard T, Jacobsen BK, Njolstad I. Trends in cardiovascular risk factors across levels of education in a general population: is the educational gap increasing? The Tromso study 1994-2008. *J Epidemiol Community Health* 2014;**68**:712–719.
30. Paalanen L, Prattala R, Laatikainen T. Contribution of education level and dairy fat sources to serum cholesterol in Russian and Finnish Karelia: results from four cross-sectional risk factor surveys in 1992–2007. *BMC Public Health* 2012;**12**: 910-2458-12-910.

CARDIOVASCULAR FLASHLIGHT

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Chinese herbal drug natural indigo may cause pulmonary artery hypertension

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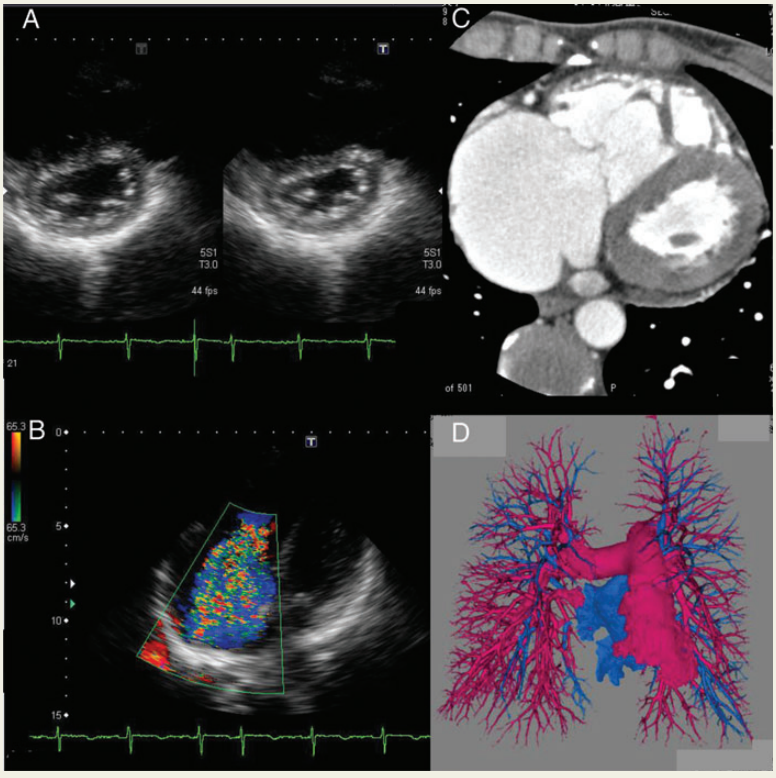

A 45-year-old woman was admitted due to increasing dyspnoea, chest oppression, and leg oedema in December 2015. She had a 5-year history of ulcerative colitis (UC) and had been taking the herbal medicine natural indigo (NI) at 2 g/day for 6 months. No abnormalities had been detected at a medical check-up 3 months before admission. On admission, transthoracic echocardiography revealed typical systolic flattening of the interventricular septum (*Panel A*) with a dilated right ventricle and severe tricuspid regurgitation (*Panel B*), indicating severe pulmonary artery hypertension (PAH). Electrocardiogram-gated contrast-enhanced computed tomography revealed a dilated right ventricle without pulmonary embolism (*Panels C* and *D*). No cardiovascular anomaly or arteriovenous shunt was detected on transoesophageal echocardiography. After diuretic treatment for 6 days, catheterization revealed PAH (58/25 mmHg; mean, 36 mmHg) and high PA resistance (689 dyn s cm^{-5}) with normal pulmonary capillary wedge and left ventricular end-diastolic pressures (5 mmHg, respectively). From the physical examinations and laboratory data, collagen diseases were considered unlikely. The lymphocyte transformation test, which indicates drug allergy, showed a positive reaction for NI, suggesting NI as a possible cause of PAH. Although symptoms were improved after diuretic therapy, estimated PA systolic pressure after discontinuing NI for 1 month remained high (58 mmHg). Careful observation and additional medication are needed.

Natural indigo, an unapproved Chinese herbal drug used for UC, has been reported as effective against intractable UC, and clinical trials are ongoing. Although no causative relationship between NI and PAH has been established, clinicians should recognize a potential association between NI and PAH.

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