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.
Introduction

Ischaemic heart disease (IHD) deaths in Sweden have decreased 55–60% due to improved risk factor patterns, mainly lower cholesterol levels. Reduction of total cholesterol by 1 mmol/L is associated with 33% lower IHD mortality among those 50–69 years of age. 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.

In high-income countries in Western Europe, cholesterol levels have decreased 0.2 mmol/L per decade since 1980, although with a slower decrease in the USA. In northern Sweden, cholesterol levels declined 0.9 mmol/L between 1986 and 2009. 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. Diet changes explain most of the early decrease in cholesterol, and statins have probably contributed only recently. 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, 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. 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 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...
<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 \(\approx 30\%\). 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 (proportion with drugs \(\times\) effect of drugs in clinical praxis/estimated reduction in cholesterol level) suggested that lipid-lowering drugs accounted for \(\approx 31\%\) of the reduced cholesterol levels between 1994 and 2014 in the 25–74 years age group, and \(\approx 44\%\) 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 \( \geq 30 \)) 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 \( \leq 25 \)), 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 \( \leq 30 \)) in the two oldest age groups (>54 years).

Among obese participants, the observed use of lipid-lowering drugs increased from 1.1% (CI 0.0–2.3) 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.
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. 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. Changes in diet have been the major driving force in northern Sweden in the MONICA and VIP studies, 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 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 range of cholesterol levels.
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.7 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 \(< 2.5 \text{mmol/L}\) 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 stable28 or diminishing7,29 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. 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 1994 to 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 to also 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. Improvements in these measures are the most effective way to combat CVD.

Authors’ contributions

M.Er. performed statistical analysis. M.EI., 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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References


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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