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A victory for statins or a defeat for diet policies? Cholesterol falls in Poland in the past decade: A modeling study ☆

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ABSTRACT

Aim: The present study is aimed to examine whether recent changes in population total cholesterol (TC) levels in Poland might be attributed to increased use statins.
Methods: Two independent, nationally representative cross-sectional studies were conducted in adults aged 18–79 years in 2002 (n = 2993, mean age 46.2 years) and 2011 (n = 2413, mean age 45.8 years), including measurements of TC in venous blood samples. The mean change of TC between 2002 and 2011 was assessed. Then the expected therapeutic reduction in TC level in 2011 attributable to statins only was calculated based on already published statin effectiveness data. Uncertainty was quantified using probabilistic sensitivity analysis.
Results: Statin uptake in Poland rose to 11.2% in 2011 (95% Confidence Intervals (CI): 10% to 12.5%) and approximately 32% (95% CI: 28.4 to 36.0%) in subjects aged 60–79 years. Mean TC in Poland in 2002 was 5.35 mmol/l, and fell by 0.21 mmol/l (95% CI: 0.14 to 0.28) by 2011. This fall would have been only 0.03 mmol/l (95% CI: −0.04 to 0.10) for the total adult population and 0.06 mmol/l (95% CI: −0.09 to 0.22) in people aged 60–79 years if statins had not been used. Statin use thus apparently explained approximately 85% (95% CI: 49% to 120%) of the observed decrease.
Conclusion: Between 2002 and 2011, statin medications apparently explained a large part of the observed fall in population cholesterol level, suggesting very little changes in population TC attributed to dietary changes.

1. Introduction

Cholesterol changes in populations are important drivers of trends in cardiovascular (CVD) mortality worldwide. Cholesterol reductions explain a substantial fraction of the observed decrease in coronary heart disease (CHD) mortality in many northern and central European populations including Finland (37%) [1], Iceland (32%) [2], Czech Republic (39.5%) [3], Sweden (39.5%) [4] and Poland (39%) [5]. Diet, especially the intake of saturated fats and trans fats has a well-established role in driving trends in cholesterol levels [6,7], which explains why substantial falls in population level total cholesterol (TC) were observed even before statins were widely in clinical use [8,9].

During recent years, the use of lipid lowering pharmacological treatments has increased substantially, mainly statins. These drugs are highly effective in managing hypercholesterolemia in individual patients and have proven to be safe [10]. However, their role in driving reductions in population cholesterol level is still unclear. For example, studies from Iceland [11], Sweden [12], Finland [13] and Czech Republic [14] do not attribute substantial cholesterol level reductions to statins, while data from the United States (US) NHANES study shows that statins probably had an impact on the US population in recent years [15].

Poland experienced dramatic epidemiological changes after the political and economic transformation during the early nineties. As a result of changes in the relative prices of different food products, the ratio of saturated to unsaturated fats in the diet decreased, associated with a sharp decline in population cholesterol level, and a large fall of the CHD mortality [5,16]. This phenomenon was not unique to Poland and was observed also in the Czech Republic [3,17] and possibly also

☆ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Slovakia, Hungary and Romania, where similar reversals of the CVD mortality trends were observed [18].

Since then, CVD mortality in Poland has continued to decrease, along with cholesterol levels. Concurrently, no concerted and effective population-level strategies to improve diet have been implemented, and the use of lipid lowering drugs has increased substantially.

In this paper, we investigate the contribution of the increasingly widespread use of statins to the recent falls in total cholesterol in the Polish population between 2002 and 2011, and indirectly estimate the contribution of other factors, mainly diet, to this fall.

2. Methods

2.1. The surveys

We conducted two independent nationally-representative, cross-sectional studies in 2002 and 2011. Research participants were randomly recruited using multistage, stratified (by age, sex and place of living) and clustered sample design. In the first stage, 60 territorial strata were defined according to geographic location and population density. Then, in each territorial stratum municipalities were drawn, each with a probability proportional to their population sizes. In each municipality, streets (in urban municipalities) and villages (in rural ones) were randomly selected. In the last stage, individual respondents were drawn, using the PESEL database (Polish Universal Electronic System for Registration of the Population). More detailed information about the sampling procedure is already described elsewhere [19,20].

In this analysis we used only data for subjects aged 18–79 years. There were no other exclusion criteria, except that the citizens who were not living at their official addresses were not interviewed and were treated as non-respondents.

The studies consisted of trained nurses visiting respondents' homes to administer a questionnaire and to measure blood pressure. Venous blood samples were collected at patients' homes at fasting state to measure biochemical risk factor measurements (i.e., fasting serum cholesterol, C-reactive protein (CRP)).

In the questionnaire, participants were asked about all drugs they took over the two weeks before the survey visit. It was strongly emphasized to patients that they should report only drugs that they took, rather than drugs prescribed by their doctor but not taken. Participants were asked to show the nurse the packages of the tablets they were taking. Finally, the name and the dose of the medication, as well as the number of doses that were actually taken, were recorded. Participants were reassured that their doctors would have no access to the data collected.

The blood samples were centrifuged in local laboratories within a maximum of 2 h from collection; serum was then frozen (−20 °C) and transported to the central laboratory. Cholesterol level was measured using the similar enzymatic method in both surveys on the Hitachi 911 (Roche Diagnostics) in 2002 and the Architect c8000 (Abbott Laboratories) in 2011.

Finally, to calculate response rate we divided the number of participants with completed questionnaire and cholesterol measurements by the number of subjects who were attempted to be contacted (with exclusion of outdated address data and subjects who died before survey visit). Both samples were weighted to correct age and sex structure to demographic structure of Polish population in 2011.

2.2. Modeling the effect of statin use on cholesterol levels

We first calculated the change in mean TC between 2002 and 2011 as the absolute difference between the observed values in these two years by sex and age group (18–39, 40–59 and 60–79 years). Then, for each individual in the study taking statins in 2011, we estimated an expected value of TC concentration if no statins would be taken, using the following formula:

$$Expected = Observed * \frac{1}{\left(1 - d_{ij}\right)}$$

where *Expected* is the expected value of TC concentration in 2011 if statin would have not be used, *Observed* is the observed value of TC concentration in 2011 and d_{ij} is the relative change of TC concentration due to use of the specific drug (i) at specified dose (j). Used values of d_{ij} were extracted from existing meta-analyses and trials, taking into account specified drugs and doses in all combinations observed in study subjects [21–23]. We assumed that effect of statins was independent of time. This is supported by a finding that this effect remains more or less stable when compared to longer and shorter lasted trials [22]. For more details please see Technical Appendix Table 1.

We aggregated *Expected* by sex and age group and calculated the change with respect to the observed 2002 levels. We aimed to estimate the mean TC level as it would have been in 2011 without the decrease driven by changes in statin use from 2002. In this analysis we assume a negligible use of statins in 2002, as statin uptake was not assessed at this time, but there is evidence to suggest that the drugs were used rarely, and mostly in very high risk individuals due to the high cost for patients. For example, statin sales data shows a 6.8-fold increase in the total weight of active substance sold in pharmacies in Poland between 2002 and 2011, from less than 3 tones to more than 19 tones. This was accompanied by a switch from less effective drugs (lovastatin) to more effective drugs (atorvastatin, simvastatin and rosuvastatin) [24].

We also assumed that our patients mostly reported drugs they really took, rather than drug prescribed by their doctor. To check this assumption, we calculated the amount of statins consumed in 2011 from our survey (assuming 100% compliance) and compared this number to the sales data [24]. This showed that our survey reported 11.943 tons of used atorvastatin and 9.046 tons of simvastatin. The corresponding masses of these drugs sold in pharmacies were 11.089 tons and 8.042 tons [24]. Atorvastatin and simvastatin represent more than 90% of the statins used in 2011 [24]. Thus, our comparison indicated little difference between the amounts of drug sold and actually reported as taken. However, we also explored in sensitivity analysis the implications of assuming that 20% of subjects who declared taking statins were actually not taking these drugs.

Finally, since statins are known to decrease CRP levels, a substantial change in CRP should parallel the effect of statins if they played an important role in driving cholesterol reductions. In order to test this hypothesis, we compared the change of CRP levels in the population between 2002 and 2011, quantifying the pattern of change across ages using local polynomial regression [25].

2.3. Handling uncertainty

We incorporated the uncertainty in survey sampling and in the expected change in TC levels due to statin use by conducting a probabilistic sensitivity analysis.

Specifically, we estimated the statin effect for each participant stochastically. The statin effect was estimated from sampling a normal distribution with mean equal to the effect of specific statin and standard deviation equal to the standard error of the effect. We iterated the process 10,000 times and then we recalculated mean expected change in TC levels due to statin use. During each recalculation mean TC change and its standard error were calculated, and result value was drawn from Gaussian samples using numbers above. Then, from 10,000 runs we found values for 2.5 and 97.5 percentiles, and reported them as 95% confidence limits. Mean total cholesterol in age and gender groups and its 95% confidence limits were calculated for 2002 and 2011 (accounting