DOI:
10.1093/gerona/glx184

TRAJECTORY OF TOTAL CHOLESTEROL IN THE LAST YEARS OF LIFE OVER AGE 80 YEARS. COHORT STUDY OF 99,758 PARTICIPANTS

Judith Charlton MSc,[a] Rathi Ravindrarajah PhD,[a] Shota Hamada DrPH,[a,b] Stephen H. Jackson MD,[c] Martin C Gulliford MA,[a,d]

[a]King's College London, Department of Primary Care and Public Health Sciences, London, UK;

[b]Research Department, Institute for Health Economics and Policy, Association for Health Economics Research and Social Insurance and Welfare, Tokyo, Japan;

[c]King's College London, Department of Clinical Gerontology, London, UK;

[d]National Institute for Health Research Biomedical Research Centre at Guy's and St Thomas' National Health Service Foundation Trust, London UK

Short title: Cholesterol trajectory over 80 years

Correspondence: **Martin Gulliford MA**

King's College London,

Department of Primary Care and Public Health Sciences,

Addison House, Guy's Campus, London, SE1 1UL, UK

Tel: +44 207 848 6641

Fax: +44 207 848 6620

Email: martin.gulliford@kcl.ac.uk

ABSTRACT

Background: Epidemiological studies suggest that lower total cholesterol (TC) may be associated with higher mortality. This study aimed to evaluate whether a decline in total cholesterol before death might account for the association of TC with mortality over age 80 years.

Methods: Cohort study using primary care electronic health records of 99,758 participants aged 80 to 105 years from the UK Clinical Practice Research Datalink (CPRD). Hazard ratios (HR) for all-cause mortality were adjusted for age, gender, frailty, comorbidity, blood pressure and smoking. Fractional polynomial models were fitted to evaluate longitudinal trends in TC before death or end-of-study. Adjusted odds ratios were estimated using generalised estimating equations.

Results: There were 63,630 women and 36,128 men, mean age 86 years, with 29,200 deaths. There were 41,164 treated with statins at cohort entry. Compared with TC values of 4.5 to 5.4 mmol/L, TC values <3.0 mmol/L were associated with higher mortality (statin treated HR 1.53, 95% confidence interval 1.43 to 1.64, P<0.001; not treated, 1.41, 1.29 to 1.54, P<0.001). A secular decline in TC values accelerated in the last two years of life. In the last quarter of follow-up, the adjusted odds of TC<3.0 mmol/L for those who died, compared with surviving participants, were 3.33 (2.84 to 3.91, P<0.001) for untreated and 1.88 (1.68 to 2.11, P<0.001) for statin treated participants.

Conclusions: TC values show a terminal decline in the last years of life. Reverse causation may contribute to the association of lower TC with higher mortality in non-randomized studies.

Key words: cardiovascular disease, frailty, statins, terminal decline, total cholesterol

Abbreviations

BP	blood pressure
CPRD	Clinical Practice Research Datalink
CVD	cardiovascular disease
FP	fractional polynomial
LDL	low-density lipoprotein
TC	total cholesterol
UK	United Kingdom

BACKGROUND

A long-term decline in cardiovascular mortality has been associated with increasing longevity. People aged more than 80 years now represent the most rapidly increasing sector of the population in many high-income countries.(1) Cardiovascular diseases are now more frequent at older ages (2) and this poses important questions for cardiovascular disease (CVD) prevention strategies for people aged 80 years and over. Hypertension, hypercholesterolaemia and smoking are recognized as the leading risk factors for cardiovascular diseases but, while smoking cessation may be advocated at any age, the role of antihypertensive and cholesterol-lowering therapy at advanced ages is more controversial.

The results of hypertension treatment trials in people aged more than 75 (3,4) or 80 years (5) suggest that blood pressure-lowering may be associated with lower mortality and fewer cardiovascular events in these age groups. This evidence conflicts with the findings of non-randomized epidemiological studies which generally show that lower blood pressure (BP) values are associated with higher mortality in older people.(6,7) We recently analysed systolic BP trajectories in people aged ≥80 years. These analyses revealed that systolic BP undergoes a 'terminal decline' in the last 24 months of life.(8) This observation suggests that the association of lower BP with higher mortality in observational studies may be accounted for by reverse causation, if people with lower BP values are generally closer to the end of life.(8) A process of terminal decline has been suggested previously in studies of physical and cognitive functioning (9-12) but the concept has not previously been applied in studies of cardiovascular risk factors.

There is strong evidence that cholesterol-lowering with statins is associated with reduced mortality and fewer cardiovascular events in primary and secondary prevention populations.(13,14) The results of these clinical trials have led to increased prescribing of statins in the general population,(15) and statin prescribing is now spilling over into the oldest age groups.(16) However, Petersen et al. (17) concluded that there was no evidence from clinical trials that cholesterol-lowering treatment was associated with lower mortality in people aged more than 80 years. This lack of evidence is concerning because non-randomized studies suggest that lower cholesterol levels might be associated with greater mortality in people aged more than 80 years.(17) In a review of 12 observational studies, Petersen et al.(17) found that the majority of cohort studies find that lower total cholesterol (TC) values are associated with higher all-cause mortality, and with higher cholesterol values being associated with lower mortality.(18) Data from some studies suggest a U-shaped, or reverse J-shaped association, of TC (17,19) or low-density lipoprotein (LDL) cholesterol with all-cause mortality in the elderly. (20) While some authors suggest that cholesterol may not be a risk factor for mortality in old age,(20) other commentators have emphasised the potential for reverse causation, if serious illness is associated with declining TC values.(21)

We hypothesized that serum TC values may show a terminal decline in old age, as was reported for systolic BP.(8) This study therefore aimed to analyse the association of TC level with mortality in people aged 80 years and older. We explored whether serum TC values undergo a terminal decline that might in part account for any associations of lower TC values with higher mortality. We investigated a large cohort of people aged 80 years and older, with stratified sampling to ensure representation of individuals up to 105 years of age.

METHODS

Study Design

A population-based cohort study was conducted in the UK Clinical Practice Research Datalink (CPRD). The CPRD is the world's largest database of primary care electronic health records, covering approximately 7% of the UK family practices.(22) The CPRD population is considered to be representative of the UK population; the database includes comprehensive data for drug prescriptions and diagnoses recorded in primary care, which have been shown to be valid in many studies.(22,23)

Study Participants

The sample was drawn from a complete listing of patients registered in CPRD as sampling frame. Stratified sampling by age and study year was employed to ensure adequate representation of older ages. Eligible participants were selected from patients aged at least 80 years old and registered with the UK Clinical Practice Research Datalink (CPRD) at any time between 1st January 2001 and the 31st December 2015. For each calendar year from 2001 to 2015, and for each single year of age from 80 to 105 years, up to a maximum of 1,000 patients were sampled from the population of patients registered during that year. The sampling procedure yielded fewer than 1,000 participants at older ages and some participants were sampled in more than one year. The sampling procedure yielded a total of 212,566 individual participants whose primary care electronic health records were analysed for this study. We restricted the analysis to the first five years from cohort entry.

Study Measures

The main measures for the study were statin prescriptions, serum TC and all-cause mortality. Statins were considered as a single group based on all statins available for prescription between 2001 and 2015. Records for serum TC (mmol/L) were obtained from values recorded into primary care electronic records. The mean of all TC records during follow-up was included in the analysis using the categories <3.0, 3.0-3.4, 3.5-4.4, 4.5-5.4 and ≥5.5 mmol/L. All-cause mortality was analysed using the date of death recorded into CPRD. Covariates were gender, five-year age group, co-morbidity and frailty category. Co-morbidity was determined from analysis of Read medical codes, and where appropriate drug product codes, for diabetes mellitus, coronary heart disease, stroke, chronic obstructive pulmonary disease, dementia, digestive disorders and musculoskeletal disorders as reported previously.(24) Frailty status was assessed using a previously published 36-item electronic Frailty Index (eFI).(25) The eFI was devized from the cumulative deficit frailty model with the eFI score calculated by the presence or absence of individual deficits as a proportion of the total possible.(26) Quantitative traits, including BP, and polypharmacy were omitted from the eFI score for this study. Categories of fit, mild, moderate and severe frailty were defined following Clegg et al.(25) Participants' smoking status was evaluated using the most recent records into the categories 'current smoker', 'ex-smoker', 'non-smoker or not recorded'. Systolic BP records were classified into the categories <110, 110-119, 120-139, 140-159 and ≥160 mm Hg, using the mean of all records during follow-up.

Analysis

The cohort was described by tabulating covariates by TC category and baseline statin treatment status. We evaluated the association of TC category with mortality in survival analyses. Since the distribution of TC differs substantially according to statin treatment status, participants were divided into those treated or not treated with statins at baseline. Participants were classified as statin treated if they received one or more statin prescriptions within the first 12 months of cohort entry. Kaplan-Meier curves were plotted to present the univariate association of TC category with all-cause mortality according to baseline statin treatment status. Cox proportional hazards models were fitted, separately for patients treated with statins and those not treated with statins. Univariate hazard ratios were estimated; then adjustment was made for age, gender and frailty category; finally, comorbidities, systolic BP category and smoking status were included. The proportional hazards assumption was evaluated using the Schoenfeld residuals. The analysis was conducted using the R program, using the 'survival' and 'survminer' packages.(27)

We evaluated the trajectory of TC over five years' follow-up, including all TC values recorded up to the date of death or end of study. For each month of follow-up, we estimated the mean TC value for each participant. Data for each participant month were classified as statin treated if participants had received a statin prescription in the previous 90 days. We used scatter plots to compare changes in mean TC values over time for participants who died by the end of the study and participants who remained alive. Data were smoothed with moving averages using three successive observations. We fitted second-order fractional polynomial (FP) models to evaluate trends in TC over time before death or end of study using mean TC values for each participant month as observations. (28) The month from five years

before death to the end of study was included in FP models as a continuous predictor with values ranging from -60 to -1. FP models were adjusted for age, gender and frailty category. Models were fitted using the 'mfp' package in the R program. (28) Predicted values and their 95% confidence intervals were estimated and overlaid on the scatterplot of empirical values. The relative odds of TC <3.0 mmol/L for deceased participants, compared with those who were alive at end of study, were estimated using the method of generalised estimating equations. Odds ratios were adjusted for age, gender and frailty category and clustering by participant.

RESULTS

The initial cohort comprised 212,566 participants of whom 99,758 (47%) had one or more TC records within five years of entry to the study. A flowchart is shown in Supplementary Figure 1. The remaining analyses include 99,758 participants including 36,128 (36%) men and 63,630 (64%) women aged 80 years or older. There were 58,594 patients not treated with statins and 41,164 patients treated with statins. There were 29,200 deaths during follow-up including 18,052 in non-users of statins and 11,148 in statin-users.

Table 1 presents the characteristics of participants divided by serum TC level. TC decreased with age, but there was only one year difference in age between highest and lowest categories. In the highest TC category, 82% of participants were women, while only 34% of the lowest TC category were female. Lower TC values were associated with greater frailty, 55% of participants with TC less than 3.0 mmol/L had moderate or severe frailty, compared with 30% of those with TC ≥5.5 mmol/L. Participants with secondary prevention indications,

including diabetes mellitus, coronary heart disease and stroke were more highly represented in the lower TC categories, while trends were less marked or absent for other comorbidities. Low TC values were also strongly associated with lower systolic BP category and stronger association with previous smoking.

Table 2 shows the distribution of covariates according to statin treatment status. As expected, statin treated participants had generally lower TC values. Statin treated participants also tended to be younger, were more frequently male, with greater levels of frailty and more frequently had comorbidities, especially secondary prevention indications including diabetes, coronary heart disease and stroke.

Figure 1 presents Kaplan-Meier curves by TC category for participants who were treated or not treated with statins. During the five- year period of follow-up, there was a graded association of lower TC category with higher mortality. Participants with TC values <3.0 or 3.0-3.4 had higher mortality than participants with TC values of 4.5-5.4 or ≥5.5 mmol/L. This pattern of association was generally similar in statin treated or untreated participants.

Table 3 presents hazards ratios from the proportional hazards models. In univariate analyses, using TC values of 4.5-5.4 mmol/L as reference, there was a graded association of lower TC values with greater mortality. For participants with TC <3.0 mmol/L, the relative hazard was approximately two times higher than reference for both statin treated and untreated participants. Adjustment for age, gender and frailty category reduced hazard ratios, but the

graded negative association of TC category with higher mortality remained. After further adjustment for comorbidities, systolic BP and smoking category, the adjusted hazard ratio for the lowest TC category was 1.41 (95% confidence interval 1.29 to 1.54) in participants not treated with statins and 1.53 (1.43 to 1.64) in participants treated with statins. In univariate analyses, there was evidence that the proportional hazards assumption for TC category did not hold either for statin treated (chi-square 33.8, P<0.001) or untreated participants (chi-square 26.2, P<0.001). For adjusted analyses in participants treated with statins, there was no evidence that the proportional hazards assumption was invalid, except for systolic BP category. For participants not treated with statins, there was evidence that the proportional hazards assumption did not hold for frailty category, systolic BP category, comorbidities of diabetes and cancer, with less strong evidence for non-proportionality with respect to TC category. The reported hazard ratios can be interpreted as the average effect over the duration of follow-up.

There were 262,518 participant months with TC values recorded. The median number of participants contributing data per month was 4,446 (range 1,934 to 6,480). There was a median of two months per participant with TC values recorded (range one to 34). Figure 2 presents a plot of TC values by month from 60 months to one month before death or end of study. Points represent the mean of TC values recorded in that month, smoothed as moving averages; shaded bands represent the 95% confidence limits for predicted values from the multiple fractional polynomial model. There is generally good agreement between empirical and predicted estimates. Data for participants treated with statins show generally lower TC values than for participants not treated with statins. In participants who did not die during follow-up, shown in blue, there is a declining secular trend in TC values over time but the data points appear to fit a linear trend. Participants who died during the five-year study period

show lower TC values throughout the period. However, data points fit a declining curve with TC values showing an accelerated decline during the final 24 months of life. Supplementary Table 1 presents the transformations and coefficients selected for the multiple FP models. Cubic terms were selected as best fit to data for participants who died, while square or inverse square terms were selected for participants who remained alive during the study period.

In the last three months of life, in participants not treated with statins at baseline, 11.3% of women and 23.3% of men had TC values <3.0 mmol/L compared with 3.6% of women and 8.0% of men who did not die (Supplementary Table 2 and Supplementary Figure 2). In the last quarter of follow-up, the adjusted relative odds of TC<3.0 mmol/L for those who died, compared with surviving participants, were 3.33 (2.84 to 3.91, P<0.001) for untreated and 1.88 (1.68 to 2.11, P<0.001) for statin treated participants.

DISCUSSION

Main findings

These non-randomized data confirm an association of lower TC values with greater mortality in people aged more than 80 years. There was a strong univariate association of TC values <3.0 mmol/L or 3.0-3.4 mmol/L with increased mortality. This association was partly accounted for by confounding with frailty, comorbidity, BP and smoking but even in adjusted analyses there was evidence that mortality might be 40-50% higher in those with TC<3.0 mmol/L compared with 4.5-5.4 mmol/L as reference. We noted that there was evidence that the proportional hazards assumption did not hold in certain analyses. This might suggest that the significance of low TC values might vary over time before death. Longitudinal analysis of

TC values in relation to date of death suggested that there is a terminal decline in TC values in the last 12-24 months of life, as we have reported previously for systolic BP.(8) This observation raises the possibility that the association between low TC and mortality might be accounted for in part by reverse causation because patients with lower TC values may be closer, on average, to the end-of-life. This might account for the lack of consistency between observational studies and randomized controlled trials in the association of TC with mortality. In randomized trials, participants in each trial will on average have a similar expected proximity to death, which may not be the case when comparison groups are assembled in observational studies. However, we caution that there are several potential explanation for the association of lower cholesterol with proximity to death with some writers associating elevated cholesterol with protection against infection(29) and improved immune defences. (30)

Comparison with other studies

Petersen et al.(17) noted that most outcome trials of lipid-lowering therapy have been conducted in patients who are considerably younger than 80 years. (31) However, meta-analyses of data for participants aged ≥65 years suggest statin therapy may reduce mortality when used for primary(32) or secondary prevention.(33) Petersen et al. (17) conducted a systematic review and found consistent evidence from non-randomized studies that lower TC values are associated with higher mortality in people aged more than 80 years. The same pattern of association has been reported for LDL-cholesterol values,(20) and for older people with type 2 diabetes mellitus (34) and heart failure.(35) Kalantar-Zadeh et al.(35) referred to the association of elevated cardiovascular risk factors with lower mortality as 'reverse

epidemiology' and drew attention to the particular relevance of this phenomenon for very old people.(36) The mechanisms underlying this effect may include deteriorating organ functioning, diminishing nutritional status, as well as inflammatory processes.(21,35-37) Higher TC values have also been associated with recovery from disability after illness. (38) The present data underline the importance of a longitudinal perspective because TC values may not track at consistent levels over time, but rather enter a phase of more accelerated decline some months before the end-of-life. This observation suggests reverse causation as a plausible explanation for the association of lower TC values with higher mortality. The observation also raises questions concerning the appropriateness of lipid-lowering therapy at the end-of-life.

Strengths and limitations

The study had the strengths of data from a large cohort of individuals aged 80 years and over with stratified sampling ensuring representation up to the age of 105 years, drawing on a nationally representative data source in the UK. Mortality was comprehensively ascertained from dates of death recorded into primary care records. We classified patients' frailty level according to an established measure of frailty but this relied on medical diagnoses coded into electronic health records, consistent with a deficit accumulation model of frailty.(25,39) This approach may not always be consistent with assessment of a frail phenotype characterized by weight loss, weakness and low energy expenditure, though the two approaches are correlated at population level.(40) TC values were those recorded in clinical practice and we acknowledge that these suffer from several limitations. Fewer than half of all eligible participants had TC values recorded; cholesterol measurement methods were not standardized

across the cohort; data for cholesterol sub-fractions were generally not available; and measurement occasions were those selected by clinicians. Decisions to perform cholesterol tests may have been associated with confounding by indication if investigations were ordered when patients presented with illness. Consequently, patients with non-measured cholesterol values might differ from those with values recorded, consistent with a 'missing not at random' mechanism. The direction of any possible bias might be difficult to anticipate. We acknowledge that TC values were sparsely recorded during follow-up, with generally fewer than 5% of participants contributing data in each month of follow-up, with a median of two TC values per participant. Consequently, further prospective studies will be needed to confirm these observations. For survival analyses we divided patients into two groups according to baseline statin treatment. We acknowledge that treatment inception and discontinuation may have occurred during follow-up (41) but the focus of our analysis was on TC levels and not on statin treatment. When TC trajectories were evaluated, statin utilisation was evaluated for each period of follow-up. We acknowledge that there may be relevant variables that were not available for analysis. Patients' social status, social networks and income may be associated with statin prescribing and with mortality but we did not have data available for analysis. We also acknowledge that the e-frailty index is based on a cumulative deficit model of frailty. It includes common comorbidities including diabetes, heart disease, stroke and respiratory disease using distinct case definitions. Adjustment for comorbidity in addition to frailty could lead to problems of over-adjustment. However, comparison of estimates from models adjusted for frailty or frailty and comorbidity shows no difference in interpretation, though the generally lower estimates form the latter are consistent with reduced residual confounding.

Conclusions

These data from a large population-based cohort of adults aged from 80 to 105 years, confirm an association of low TC values with all-cause mortality. Longitudinal analysis of TC records reveals that TC values show a declining secular trend but there is evidence of an accelerated decline in TC values in the last 12-24 months of life, which is not observed in participants who do not die. The observation of a terminal decline in TC values suggests that reverse causation may in part account for the association of mortality with low TC in non-randomized studies.

These findings have relevance for both researchers and clinicians. These results draw the attention of researchers to the importance of studying longitudinal changes in physiological and pathophysiological measures in very old people. Such changes may be of prognostic importance and might indicate the need and potential for future intervention. In clinical contexts, these observations help to explain why randomized trial estimates may differ from those derived from observational studies, providing clinicians with reassurance that non-randomized associations of lower TC with higher mortality might not be regarded as causal, but instead accounted for by reverse causation.

Conflicts of Interest: None

Funding: This work was supported by the Dunhill Medical Trust [grant number: R392/1114]. MG was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London.

REFERENCES

1. Office for National Statistics. *Estimates of the very old (including centenarians).* London: Office for National Statistics, 2016.

2. Olshansky SJ, Ault AB. The fourth stage of the epidemiologic transition: the age of delayed degenerative diseases. Milbank Q 1986;64:355-91.

3. The SPRINT Research Group. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med 2015;373:2103-16. doi: 10.1056/NEJMoa1511939

4. Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years: A randomized clinical trial. JAMA 2016;315:2673-82. doi: 10.1001/jama.2016.7050

5. Beckett NS, Peters R, Fletcher AE et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008;358:1887-98. doi: 10.1056/NEJMoa0801369

6. Molander L, Lovheim H, Norman T, Nordstrom P, Gustafson Y. Lower systolic blood pressure is associated with greater mortality in people aged 85 and older. J Am Geriatr Soc 2008;56:1853-9. doi: 10.1111/j.1532-5415.2008.01948.x.

7. Guo Z, Viitanen M, Winblad B. Low blood pressure and five-year mortality in a Stockholm cohort of the very old: possible confounding by cognitive impairment and other factors. Am J Public Health 1997;87:623-8.

8. Ravindrarajah R, Hazra NC, Hamada S et al. Systolic Blood Pressure Trajectory, Frailty and All-Cause Mortality Over 80 Years of Age. Cohort Study Using Electronic Health Records. Circulation 2017; 35(6):1276-1282. doi: 10.1097/HJH.0000000000001291

9. Diehr P, Williamson J, Burke GL, Psaty BM. The aging and dying processes and the health of older adults. J Clin Epidemiol 2002;55:269-78.

10. Palmore E, Cleveland W. Aging, Terminal Decline, and Terminal Drop. J Gerontol 1976;31:76-81.

11. Siegler IC. The terminal drop hypothesis: Fact or artifact? Exp Aging Res 1975;1:169-185.

12. Chen JH, Chan DC, Kiely DK, Morris JN, Mitchel SL. Terminal Trajectories of Functional Decline in the Long-Term Care Setting. J Gerontol: Series A 2007; 62: 531–536, doi: 10.1093/gerona/62.5.531

13. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. The Lancet 2005;366:1267-78. doi: 10.1016/S0140-6736(05)67394-1

14. Chou R, Dana T, Blazina I, Daeges M, Jeanne TL. Statins for prevention of cardiovascular disease in adults: Evidence report and systematic review for the us preventive services task force. JAMA 2016;316:2008-24. doi: 10.1001/jama.2015.15629

15. Walley T, Folino-Gallo P, Stephens P, Van Ganse E, the EuroMedStat g. Trends in prescribing and utilization of statins and other lipid lowering drugs across Europe

1997–2003. Br J Clin Pharmacol 2005;60:543-51. doi: 10.1111/j.1365-2125.2005.02478.x

16. Johansen ME, Green LA. Statin use in very elderly individuals, 1999-2012. JAMA Internal Medicine 2015;175:1715-6. doi: 10.1001/jamainternmed.2015.4302.

17. Petersen LK, Christensen K, Kragstrup J. Lipid-lowering treatment to the end? A review of observational studies and RCTs on cholesterol and mortality in 80+-year olds. Age and Ageing 2010; 39:674-80. doi: 10.1093/ageing/afq129

18. Weverling-Rijnsburger AWE, Blauw GJ, Lagaay AM, Knock DL, Meinders AE, Westendorp RGJ. Total cholesterol and risk of mortality in the oldest old. Lancet 1997;350:1119-23.

19. Schatz IJ, Masaki K, Yano K, Chen R, Rodriguez BL, Curb JD. Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study. Lancet 2001;358:351-5. doi: 10.1016/S0140-6736(01)05553-2

20. Ravnskov U, Diamond DM, Hama R et al. Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: a systematic review. BMJ Open 2016;6: e010401 doi: 10.1136/bmjopen-2015-010401.

21. Iribarren C, Reed DM, Chen R, Yano K, Dwyer JH. Low Serum Cholesterol and Mortality. Which Is the Cause and Which Is the Effect? Ciculation 1995;92:2396-403.

22. Williams T, van Staa T, Puri S, Eaton S. Recent advances in the utility and use of the General Practice Research Database as an example of a UK Primary Care Data resource. Ther Adv Drug Safety 2012;3:89-99. doi: 10.1177/2042098611435911

23. Herrett E, Gallagher AM, Bhaskaran K et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol 2015;44:827-36. doi: 10.1093/ije/dyv098

24. Hazra NC, Dregan A, Jackson S, Gulliford MC. Differences in Health at Age 100 According to Sex: Population-Based Cohort Study of Centenarians Using Electronic Health Records. J Am Geriatr Soc 2015;63:1331-7. doi: 10.1111/jgs.13484.

25. Clegg A, Bates C, Young J et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age and Ageing 2016;45:353-60. doi: 10.1093/ageing/afw039

26. Rockwood K, Song X, MacKnight C et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173: 489-95. doi: 10.1503/cmaj.050051

27. R Core Development Team. *R: A language and environment for statistical computing.* Vienna, Austria: R Foundation for statistical computing., 2010.

28. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. Int J Epidemiol 1999;28:964-74.

29. Sijbrands EJG, Kaprio J, Westendorp RGJ et al. Mortality over two centuries in large pedigree with familial hypercholesterolaemia: family tree mortality study. BMJ 2001;322:1019-1023.

30. Ravnskov U, McCully KS. Vulnerable Plaque Formation from Obstruction of Vasa Vasorum by Homocysteinylated and Oxidized Lipoprotein Aggregates Complexed with Microbial Remnants and LDL Autoantibodies. Annals of Clinical & Laboratory Science 2009;39:3-16.

31. Taylor F, Huffman MD, Macedo AF et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013; C D004816. doi: 10.1002/14651858.CD004816.pub5.

32. Savarese G, Gotto AM, Paolillo S et al. Benefits of Statins in Elderly Subjects Without Established Cardiovascular DiseaseA Meta-Analysis. J Am Coll Cardiol 2013;62:2090-9. doi: 10.1016/j.jacc.2013.07.069.

33. Afilalo J, Duque G, Steele R, Jukema JW, de Craen AJM, Eisenberg MJ. Statins for Secondary Prevention in Elderly Patients. A Hierarchical Bayesian Meta-Analysis. J Am Coll Cardiol 2008;51:37-45. doi: 10.1016/j.jacc.2007.06.063

34. Hamada SG, MC. Mortality in Type 2 Diabetes at 80 Years or Older in Relation to HbA1c, Blood Pressure, and Total Cholesterol. J Am Geriatr Soc 2016; 64:1425-31. doi: 10.1111/jgs.14215

35. Kalantar-Zadeh K, Block G, Horwich T, Fonarow GC. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. J Am Coll Cardiol 2004;43:1439-44. doi: 10.1016/j.jacc.2003.11.039

36. Ahmadi SF, Streja E, Zahmatkesh G et al. Reverse Epidemiology of Traditional Cardiovascular Risk Factors in the Geriatric Population. J Am Med Dir Assoc. 2015;16:933-9. doi: 10.1016/j.jamda.2015.07.014.

37. Ranieri R, Rozzini S, Franzoni P, Barbisoni M, Trabucchi P. Serum Cholesterol Levels as a Measure of Frailty in Elderly Patients. Exp Aging Res 1998;24:169-79.

38. Onder G, Volpato S, Liperoti R et al. Total Serum Cholesterol and Recovery From Disability Among Hospitalized Older Adults . J Gerontol: Series A, 2006; 61: 736–742. doi: 10.1093/gerona/61.7.736

39. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. The Lancet 2013;381:752-62. doi: 10.1016/S0140-6736(12)62167-9.

40. Rockwood K, Andrew M, Mitnitski A. A Comparison of Two Approaches to Measuring Frailty in Elderly People. J Gerontol Series A: Biol Sci Med Sci 2007;62:738-43.

41. Gulliford M, Ravindrarajah R, Hamada S, Jackson SH, Charlton J. Inception and deprescribing of statins in people aged over 80 years: cohort study, Age and Ageing 2017 [Epub] https://doi.org/10.1093/ageing/afx100

Table 1: Baseline characteristics of participants by total cholesterol category. Figures are frequencies (column percent)

		Total Cholesterol (mmol/L)					
		<3.0	**3.0-3.4**	**3.5-4.4**	**4.5-5.4**	**≥5.5**	**P value**
Age (years)	Mean (SD)	87 (5)	86 (5)	86 (5)	86 (5)	86 (5)	<0.001
Gender	Men	2,636 (66)	3,688 (60)	14,381 (47)	10,823 (33)	4,600 (18)	<0.001
	Women	1,341 (34)	2,475 (40)	16,464 (53)	21,883 (67)	21,467 (82)	
Frailty	Fit	439 (11)	794 (13)	5,191 (17)	7,470 (23)	7,518 (29)	<0.001
	Mild	1,377 (35)	2,223 (36)	11,783 (38)	13,183 (40)	10,554 (40)	<0.001
	Moderate	1,301 (33)	1,984 (32)	9,352 (30)	8,507 (26)	5,808 (22)	<0.001
	Severe	860 (22)	1,162 (19)	4,519 (15)	3,546 (11)	2,187 (8)	<0.001
Comorbidity	DM	1,431 (36)	1,951 (32)	7,971 (26)	5,772 (18)	2,627 (10)	<0.001
	CHD	2,010 (51)	2,884 (47)	12,199 (40)	9,532 (29)	5,182 (20)	<0.001

	Stroke	799 (20)	1,110 (18)	4,310 (14)	3,417 (10)	1,870 (7)	<0.001
	COPD	781 (20)	1,196 (19)	6,125 (20)	6,309 (19)	4,866 (19)	0.003
	Dementia	386 (10)	602 (10)	2,557 (8)	2,612 (8)	1,850 (7)	<0.001
	Cancer	994 (25)	1,403 (23)	7,099 (23)	6,894 (21)	5,011 (19)	<0.001
	Digestive	2,682 (67)	4,074 (66)	19,557 (63)	19,616 (60)	14,747 (57)	<0.001
	MSK	3,018 (76)	4,765 (77)	24,145 (78)	25,193 (77)	20,002 (77)	0.043
Smoking status	Ex-smoker	1,602 (40)	2,496 (40)	11,801 (38)	11,025 (34)	7,624 (29)	<0.001
	Current smoker	196 (5)	341 (6)	1,700 (6)	1,853 (6)	1,316 (5)	0.281
Systolic BP category (mm Hg)	<110	339 (9)	384 (6)	1,185 (4)	846 (3)	448 (2)	<0.001
	110-119	628 (16)	762 (12)	2,814 (9)	2,089 (6)	1,169 (4)	
	120-139	1,930 (49)	3,107 (50)	14,813 (48)	13,928 (43)	9,144 (35)	
	140-159	821 (21)	1,534 (25)	9,855 (32)	12,530 (38)	11,473 (44)	
	≥160	133 (3)	216 (4)	1,595 (5)	2,734 (8)	3,330 (13)	
	Not known	126 (3)	160 (3)	583 (2)	579 (2)	503 (2)	

Table 2: Characteristics of participants by baseline statin treatment status. Figures are frequencies (column percents)

		No statins (58,594)	Statins (41,164)	P value
Age (years)	Mean (SD)			
Gender	Men	19,328 (33)	16,800 (41)	<0.001
	Women	39,266 (67)	24,364 (59)	
Frailty	Fit	15,936 (27)	5,476 (13)	<0.001
	Mild	23,423 (40)	15,697 (38)	<0.001
	Moderate	13,735 (23)	13,217 (32)	<0.001
	Severe	5,500 (9)	6,774 (16)	<0.001
Comorbidity	DM	8,208 (14)	11,544 (28)	<0.001
	CHD	12,292 (21)	19,515 (47)	<0.001
	Stroke	4,888 (8)	6,618 (16)	<0.001
	COPD	10,874 (19)	8,403 (20)	<0.001
	Dementia	4,648 (8)	3,359 (8)	0.193
	Cancer	12,171 (21)	9,230 (22)	<0.001
	Digestive	33,983 (58)	26,693 (65)	<0.001
	Musculoskeletal	43,890 (75)	33,233 (81)	<0.001

Smoking status	Ex-smoker	18,572 (32)	15,976 (39)	<0.001
	Current smoker	3,142 (5)	2,264 (5)	0.345
Systolic BP category	<110	1,760 (3)	1,442 (4)	<0.001
	110-119	3,896 (7)	3,566 (9)	
	120-139	22,963 (39)	19,959 (48)	
	140-159	22,729 (39)	13,484 (33)	
	≥160	5,924 (10)	2,084 (5)	
	Not known	1,322 (2)	629 (2)	
Total Cholesterol (mmol/L)	<3.0	979 (2)	2,998 (7)	<0.001
	3.0-3.4	1,655 (3)	4,508 (11)	
	3.5-4.4	12,521 (21)	18,324 (45)	
	4.5-5.4	21,454 (37)	11,252 (27)	
	≥5.5	21,985 (38)	4,082 (10)	

Table 3: Relative hazards of all-cause mortality by total cholesterol category and baseline statin treatment in men and women aged 80 years and older.

Total Cholesterol (mmol/L)	N	Deaths	Univariate			Adjusted for age, gender and frailty			Adjusted for age, gender, frailty, comorbidity, systolic BP and smoking		
			HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
No statins											
<3.0	979	577	1.97	1.81 to 2.15	<0.001	1.66	1.53 to 1.81	<0.001	1.41	1.29 to 1.54	<0.001
3.0-3.4	1,655	853	1.46	1.36 to 1.57	<0.001	1.31	1.21 to 1.40	<0.001	1.14	1.06 to 1.22	<0.001
3.5-4.4	12,521	5,018	1.17	1.13 to 1.22	<0.001	1.10	1.06 to 1.14	<0.001	1.04	1.00 to 1.08	0.027
4.5-5.4	21,454	6,506	Ref.			Ref.			Ref.		
>5.5	21,985	5,098	0.82	0.79 to 0.85	<0.001	0.89	0.86 to 0.92	<0.001	0.95	0.92 to 0.99	0.013
Statins											
<3.0	2,998	1,322	2.19	2.05 to 2.34	<0.001	1.86	1.74 to 1.99	<0.001	1.53	1.43 to 1.64	<0.001
3.0-3.4	4,508	1,513	1.52	1.43 to 1.62	<0.001	1.36	1.27 to 1.45	<0.001	1.19	1.12 to 1.27	<0.001
3.5-4.4	18,324	4,900	1.16	1.11 to 1.22	<0.001	1.10	1.04 to 1.15	<0.001	1.05	1.00 to 1.10	0.076
4.5-5.4	11,252	2,536	Ref.			Ref.			Ref.		
>5.5	4,082	877	1.03	0.95 to 1.11	0.441	1.05	0.97 to 1.14	0.200	1.09	1.01 to 1.18	0.022

CI, confidence interval; HR, hazard ratio; N, number of participants

Legend for Figure 1: Kaplan-Meier curves by total cholesterol level for patients treated and not treated with statins. TC, total cholesterol.

3

Legend for Figure 2: Trajectory of total cholesterol during 60 months before death (red) or end of study (blue) in participants treated or not treated with statins. Data points are mean total cholesterol by month; blue squares, alive at end of study; red circles, died. Shaded areas represent 95% confidence intervals for predictions from multiple fractional polynomial model adjusted for age, gender and frailty category.

Figure 1

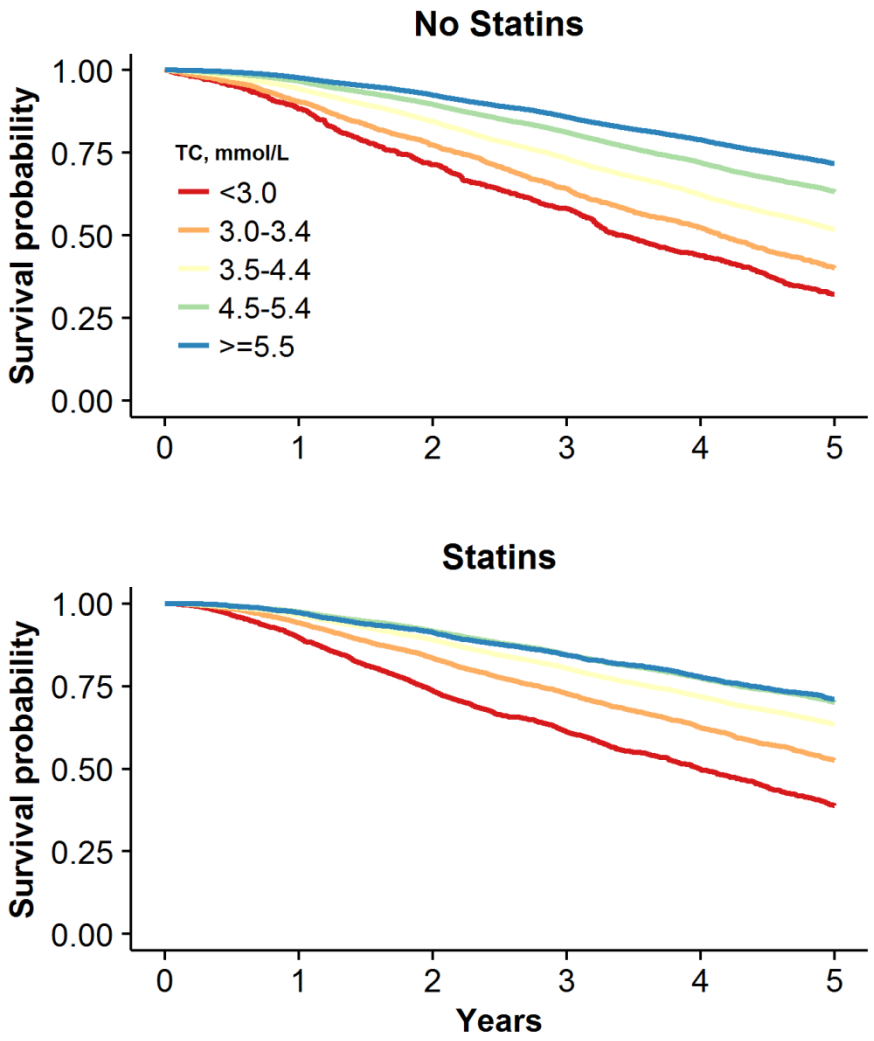

Figure 2