ApoB and Non-HDL Cholesterol Versus LDL Cholesterol for Ischemic Stroke Risk

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Objective: Conflicting results have been reported on the association between lipids and risk of ischemic stroke. We tested the hypothesis that the burden of ischemic stroke attributable to either elevated apolipoprotein B (apoB) or non-high-density lipoprotein (non-HDL) cholesterol is higher than that attributable to elevated low-density lipoprotein (LDL) cholesterol.

Methods: We included 104,618 individuals from an ongoing cohort study, the Copenhagen General Population Study. The associations of quintiles of apoB, non-HDL cholesterol, and LDL cholesterol with risk of ischemic stroke were estimated by Cox proportional hazards regressions with 95% confidence intervals. With 1st quintile as reference, the proportion of ischemic stroke attributable to the 2nd, 3rd, 4th, and 5th quintiles of apoB, non-HDL cholesterol, and LDL cholesterol were estimated by population attributable fractions.

Results: Higher quintiles of apoB and non-HDL cholesterol were associated with increased risk of ischemic stroke (both trends: $p < 0.0001$), whereas for LDL cholesterol this association was somewhat attenuated (trend: $p = 0.0005$). A similar pattern was seen for population attributable fraction values. Compared to individuals in the 1st quintile, the combined proportion of ischemic stroke attributable to individuals in the 2nd to 5th quintiles was 16.3% for apoB (levels >82 mg/dL), 14.7% for non-HDL cholesterol (>3.0 mmol/L; >117 mg/dL), and 6.8% for LDL cholesterol (>2.4 mmol/L; >94 mg/dL).

Interpretation: The proportion of ischemic stroke attributable to either elevated apoB or non-HDL cholesterol was double that attributable to elevated LDL cholesterol.

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Introduction

Stroke remains one of the leading causes of disability, morbidity, and mortality worldwide.[1,2] Among survivors of ischemic stroke or transient ischemic attack, prevention strategies include antiplatelet therapy and treatment of atrial fibrillation, hypertension, and hyperlipidemia.[3,4]

The association between high levels of low-density lipoprotein (LDL) cholesterol and high risk of cardiovascular disease, e.g., myocardial infarction, has been firmly established.[5] However, discrepant results have been found in both observational and genetic studies on elevated LDL cholesterol related to increased risk of stroke; while some studies have found an association between high levels of LDL cholesterol and increased risk of ischemic stroke[6–11] others found no association.[12–19] Several studies have found a weaker association between high LDL cholesterol levels and risk of ischemic stroke than between high LDL cholesterol and coronary heart disease.[14,16–19] Nevertheless, randomized trials have shown that lowering of LDL cholesterol by statins reduces the risk of recurrent as well as initial stroke.[20–22] Indeed, guidelines on the management of patients with stroke recommend treatment with lipid lowering therapy regardless of LDL cholesterol levels.[3,4]

Non-high-density lipoprotein (non-HDL) cholesterol, a measurement of the mass of cholesterol of all

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atherogenic lipoproteins, and apolipoprotein B (apoB), a measurement of the total number of atherogenic particles circulating in the blood, have been shown to be better markers of risk of coronary heart disease than has LDL cholesterol.[23] Thus, it is also likely that elevated non-HDL cholesterol and apoB are better markers of risk of ischemic stroke than is elevated LDL cholesterol. Most studies on high non-HDL cholesterol or apoB levels and risk of ischemic stroke have found an association[6–8,10,12–16,24,25]; however, some have found no association.[14,16,17,25] Among these, the studies that also include LDL cholesterol found the association of non-HDL cholesterol and/or apoB with risk of ischemic stroke to be more pronounced than the association of LDL cholesterol with risk of ischemic stroke.[6–8,10,12–16] To our knowledge no previous studies have compared back-to-back the burden of ischemic stroke attributable to either elevated apoB, non-HDL cholesterol, or LDL cholesterol.

In addition, no difference across sexes was found in a meta-analysis from 2016 on the association between elevated total cholesterol and risk of ischemic stroke.[26] However, studies on the association of LDL cholesterol, non-HDL cholesterol, and apoB on risk of ischemic stroke in women and men separately are limited.[7,13,14,16,17]

We tested the hypothesis that the burden of ischemic stroke attributable to either elevated apoB or non-HDL cholesterol is higher than that attributable to elevated LDL cholesterol in the overall population and in men and women separately.

Methods

Study Population

We included 104,618 individuals from the Copenhagen General Population Study. The cohort was conducted in 2003–2015 and reflects the white Danish general population as invited individuals were 20–100 years of age and randomly selected from the Danish Civil Registration System. The participants filled in a self-administered questionnaire, underwent an on-site physical examination, and had blood samples taken for biochemical analyses.

Written informed consent was given by each participant in the cohort. The study was conducted according to the Declaration of Helsinki and approved by institutional review board, the Ethics Committee of the Danish Capital Region (H-KF-01-144/01), and the Danish Data Protection Agency.

Ischemic Stroke

The national Danish Patient Registry holds information on all hospital contacts from 1977 and onwards (outpatients and emergency wards from 1995) and the national Danish Causes of Death Registry on all deaths. Diagnoses on ischemic stroke were ascertained from these registries in terms of International Classification of Disease (ICD) codes: ICD8 codes 433–434 and ICD10 code I63. Diagnoses of ischemic strokes were validated by two independent doctors by retrieving hospital journals, computed tomography (CT) scans, magnetic resonance imaging (MRI), spinal fluid examinations, procedure descriptions, and autopsies to distinguish between ischemic infarctions, intracerebral hemorrhages, and subarachnoid hemorrhages. A diagnosis of ischemic stroke was only valid in case of focal neurological symptoms lasting ≥24 hours. Symptoms consistent with a stroke event without visualization of neither an ischemic infarction nor a hemorrhage on a scan was classified as an ischemic stroke. However, if a scan visualized previous cerebrovascular disease but there were no concurrent symptoms, the individual was not ascribed a diagnosis of ischemic stroke. Hemorrhagic strokes diagnoses were excluded from the group of ischemic strokes.

Laboratory Analyses

Plasma apoB was measured by a turbidimetric assay while plasma triglycerides, total cholesterol, and high-density-lipoprotein cholesterol were measured by colorimetric assays using routine hospital auto-analyzers. Plasma LDL cholesterol was calculated using the Friedewald equation (LDL cholesterol = total cholesterol – high-density cholesterol – triglycerides/2.2 in mmol/L and LDL cholesterol = total cholesterol – high-density cholesterol – triglycerides/5 in mg/dL) when triglycerides were below 4 mmol/L (350 mg/dL). At triglyceride levels higher than this, LDL cholesterol was measured directly.

Covariates

Based on known associations of the lipid parameters apoB, non-HDL cholesterol, and LDL cholesterol with ischemic stroke, we chose the covariates for adjustment of analyses *a priori*. These covariates include sex, age, smoking status (current vs. former/never smoker), cumulated number of pack-years smoked, alcohol consumption (units per week), lipid-lowering therapy, hypertension, and atrial fibrillation. In sensitivity analyses, we further adjusted for body mass index (BMI) and diabetes as they might be in the biological pathway; however, these analyses showed results similar to the ones reported. The Civil Registration Number provides information on sex and age. In the questionnaire, the participants reported on alcohol consumption, current and former smoking habits, lipid-lowering therapy, hypertension, and diabetes. Furthermore, the participants had their height, weight, and blood pressure measured at the physical examination. BMI was calculated as weight in kg divided by height in meters squared and categorized as underweight (< 18.5), normal range (18.5–24.9),

TABLE. Baseline Characteristics of 104,618 Individuals from the Copenhagen General Population Study

	Apolipoprotein B		Non-HDL cholesterol		LDL cholesterol	
	1st-20th percentile	21st-100th percentile	1st-20th percentile	21st-100th percentile	1st-20th percentile	21st-100th percentile
mmol/L			2.6 (2.3–2.9)	4.2 (3.6–4.9)	2.1 (1.8–2.3)	3.4 (3.0–4.0)
mg/dL	73 (66–78)	113 (98–135)	101 (89–112)	163 (139–190)	82 (70–89)	132 (116–155)
Number	20,999 (20)	83,619 (80)	21,002 (20)	83,616 (80)	20,965 (20)	83,653 (80)
Age, years	52 (44–65)	59 (49–67)	54 (44–67)	58 (49–67)	56 (45–68)	58 (49–67)
Women	13,937 (66)	44,008 (53)	13,238 (63)	44,707 (53)	11,943 (57)	46,002 (55)
Current smoker	2,706 (13)	15,238 (18)	2,866 (14)	15,078 (18)	3,218 (15)	14,726 (18)
Pack-years, ever smokers	11 (4–25)	17 (7–30)	13 (5–28)	16 (6–30)	15 (6–31)	15 (6–30)
Alcohol, units	7 (3–14)	8 (4–15)	7 (3–14)	8 (4–15)	8 (3–15)	8 (4–15)
Hypertension	10,933 (52)	57,758 (69)	11,710 (56)	56,981 (68)	12,695 (61)	55,996 (67)
Lipid-lowering therapy	3,649 (17)	7,544 (9)	4,960 (24)	6,233 (7)	6,052 (29)	5,141 (6)
BMI, kg/m^2	23.6 (21.7–26.1)	26.0 (23.7–28.8)	24.0 (21.9–26.7)	25.9 (23.6–28.7)	24.7 (22.4–27.8)	25.7 (23.4–28.5)
Diabetes	1,264 (6)	2,962 (4)	1814 (9)	2,412 (3)	2,250 (11)	1976 (2)
Atrial fibrillation	1766 (8)	7,193 (9)	2009 (10)	6,950 (8)	2,235 (11)	6,724 (8)

Values are median (interquartile range) or numbers (%).
Abbreviations: BMI = body mass index; LDL = low-density lipoprotein; non-HDL = non-high-density lipoprotein.

overweight (25–29.5), and obese (≥ 30) based on WHO classification. Diabetes was defined as individuals with a registered diagnosis in the national Danish Patient Registry, a measured non-fasting plasma glucose >11 mmol/L (198 mg/dL), self-reported diagnosis of diabetes, or reporting taking antidiabetic medication; the two latter to include individuals diagnosed by their general practitioners. Individuals were ascribed a diagnosis of hypertension if having systolic blood pressure > 140 mmHg (>135 mmHg for individuals with diabetes), diastolic blood pressure > 90 mmHg (>85 mmHg for individuals with diabetes), or they reported taking antihypertensive medication.

Statistical Analyses

All statistical analyses were performed in Stata/SE 15.1.

Individuals included in this study had baseline measurements of apoB, non-HDL cholesterol, and LDL cholesterol. Furthermore, individuals with an event of ischemic stroke before baseline were excluded. The dataset was more than 99% complete concerning covariates for adjustment. Missing covariates were imputed using regression based on age and sex for continuous variables and creating a separate category for categorical variables. However, analyses on data without imputation of missing covariates yielded similar results to the ones reported.

Cox proportional hazards regressions with 95% confidence intervals (CIs) were used to estimate the association of quintiles of apoB, non-HDL cholesterol, and LDL cholesterol, respectively, with risk of ischemic stroke. Age adjustment was performed by using age as underlying time scale in the analyses and left truncation (delayed entry at study examination). Each individual was followed from the day of examination until either an ischemic stroke occurred or censoring due to emigration (n = 447), death, or end of follow-up on December 13, 2018. To meet the proportional hazards assumption tested by Shoenfeld residuals and log–log plots of survival, analyses were stratified by atrial fibrillation and sensitivity analyses furthermore by BMI categories. P for trend across quintiles within each lipid trait on risk of ischemic stroke was calculated by considering the quintiles as a continuous variable. These analyses were done in the entire cohort as well as in subgroups of individuals with and without diabetes,

hypertension, and ≥7.5% absolute 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimated by the US Pooled Cohort Equations.[27] In the stratified analyses, test for interaction was performed by inserting two-factor interaction terms (e.g., apoB quintiles as a continuous variable by diabetes on risk of ischemic stroke) in the main Cox regression analyses. Furthermore, we estimated the proportion of ischemic stroke attributable to higher quintiles of apoB, non-HDL cholesterol, and LDL cholesterol by population attributable fraction (PAF). PAF estimates were calculated using the Miettinen's formula:

$$PAF = P(1 - 1/HR)$$

P is the prevalence of the risk factor among cases and HR is the hazard ratio of that risk factor.[28] We chose Miettinen's formula over Levin's formula because only unadjusted relative risk estimates are valid in the latter, whereas adjusted hazard ratios are valid relative risk estimates in Miettinen's formula.[28,29] However, PAF estimates by Levin's formula showed similar results to the ones reported. In this study, multivariable adjusted hazard ratios with 1st quintile as reference were used in the formula to estimate PAFs for the 2nd, 3rd, 4th, and 5th quintiles. In addition, to evaluate the proportion of ischemic stroke attributable to all apoB, non-HDL cholesterol, and LDL cholesterol levels above the 1st quintile, the PAF estimates for the 2nd to 5th quintiles were summed. For the latter PAF estimates, CIs were estimated using the punafcc command in Stata. The above-mentioned PAF values were estimated within the overall population, in women and men separately, and in subgroups of individuals with diabetes, hypertension, and ≥7.5% absolute 10-year ASCVD risk. The quintiles used in all subgroup analyses were the same as for the overall population.

Results

This study included 104,618 individuals free of ischemic stroke at baseline and with measurements of apoB, non-HDL cholesterol, and LDL cholesterol. During a median follow-up of 9.2 years (interquartile range 6.4–11.7), 2,784 individuals experienced their first ischemic stroke at a median age of 69 years (interquartile range 61–76 years). Table shows baseline characteristics by 1st–20th percentile (1st quintile) and 21st–100th percentile (2nd to 5th quintiles pooled) of apoB, non-HDL cholesterol, and LDL

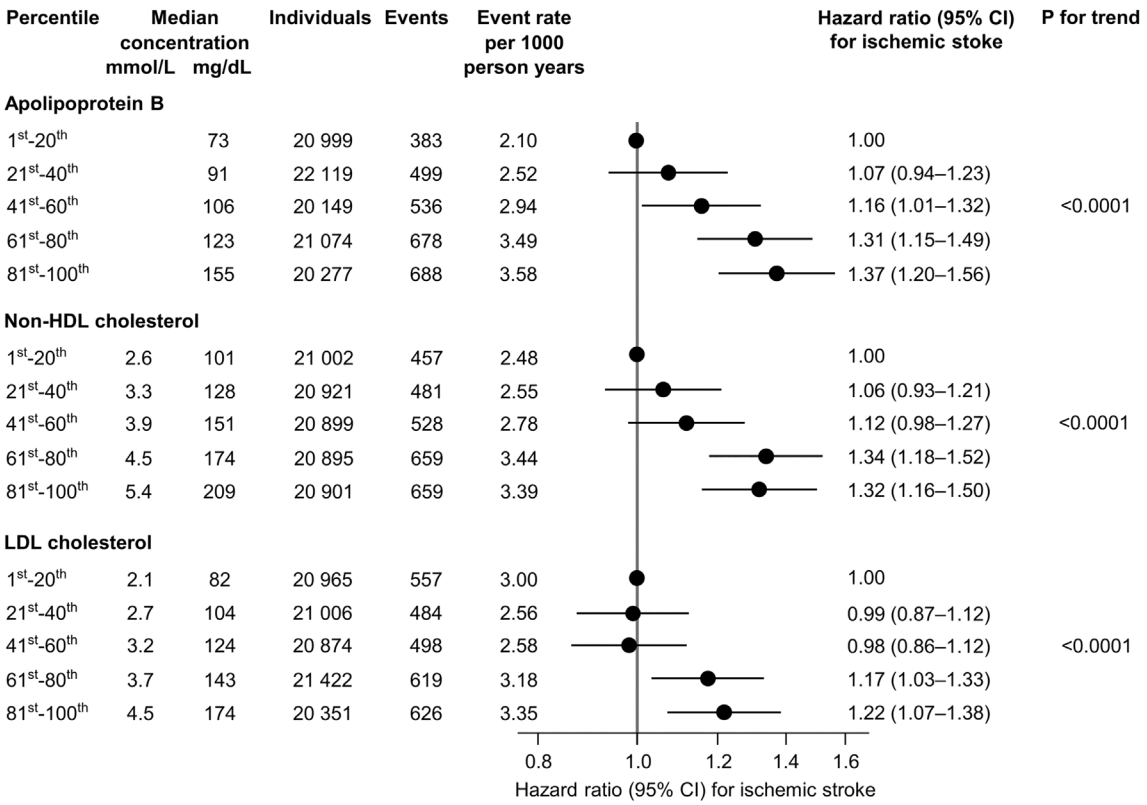

FIGURE 1: Multivariable adjusted hazard ratios for ischemic stroke according to quintiles of plasma apolipoprotein B, non-HDL cholesterol, and LDL cholesterol. Analyses were adjusted for age, sex, smoking status, pack-years, alcohol intake, hypertension, lipid-lowering therapy, and atrial fibrillation. Based on individuals from the Copenhagen General Population Study. Abbreviations: CI = confidence interval; LDL = low-density lipoprotein; non-HDL = non-high-density lipoprotein.

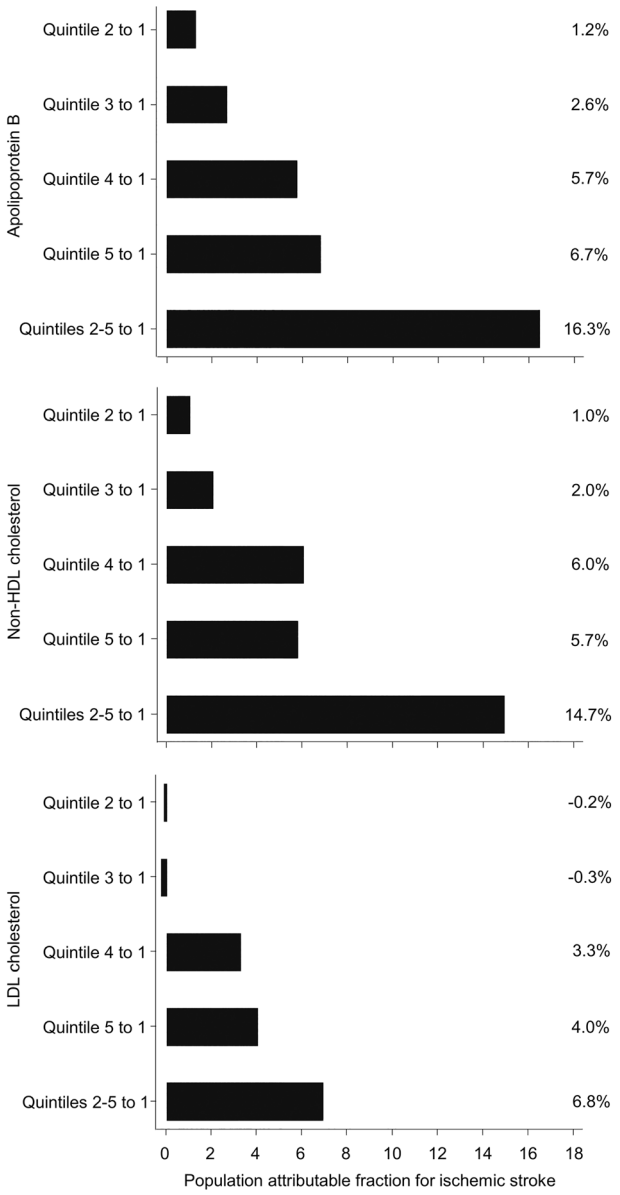

FIGURE 2: Population attributable fraction of ischemic stroke for quintiles of plasma apolipoprotein B, non-HDL cholesterol, and LDL cholesterol. Calculations by Miettinen's formula were based on multivariable adjusted hazard ratios. Analyses were adjusted for age, sex, smoking status, pack-years, alcohol intake, hypertension, lipid-lowering therapy, and atrial fibrillation. Based on 104,618 individuals with 2,784 ischemic stroke events from the Copenhagen General Population Study. Abbreviations: LDL = low-density lipoprotein; non-HDL = non-high-density lipoprotein.

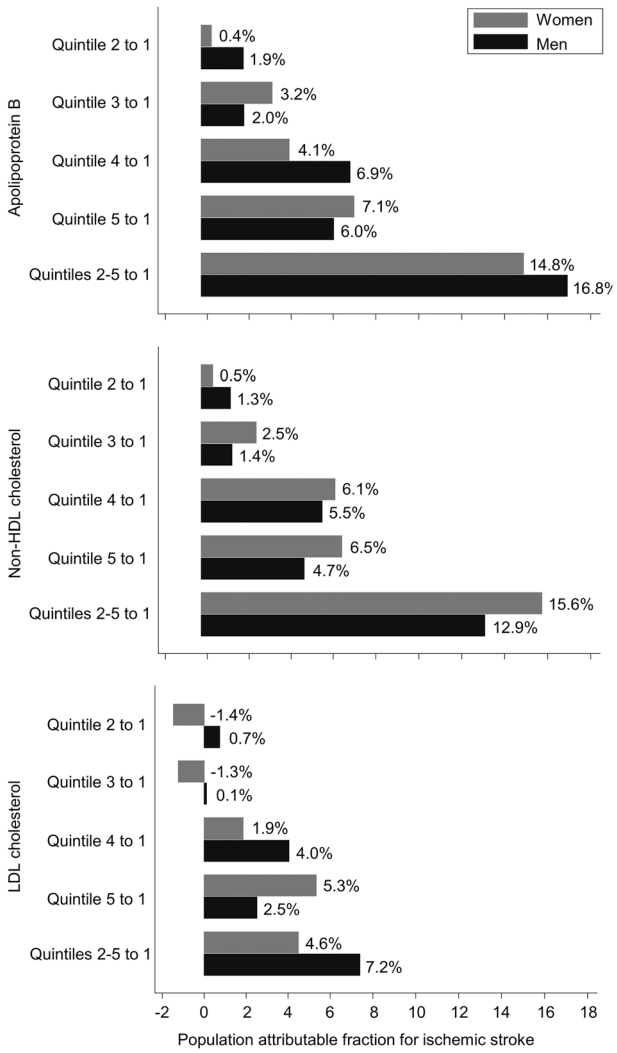

FIGURE 3: Population attributable fraction of ischemic stroke for quintiles of plasma apolipoprotein B, non-HDL cholesterol, and LDL cholesterol in women and men. Calculations by Miettinen's formula were based on multivariable adjusted hazard ratios. Analyses were adjusted for age, sex, smoking status, pack-years, alcohol intake, hypertension, lipid-lowering therapy, and atrial fibrillation. Based on 57,945 women and 46,673 men with 1,278 and 1,506 ischemic stroke events, respectively, from the Copenhagen General Population Study. Abbreviations: LDL = low-density lipoprotein; non-HDL = non-high-density lipoprotein.

cholesterol. In general, individuals in the 1st quintiles were younger, more often women, less were smokers, fewer had hypertension, and more had lower BMI; this was most pronounced for apoB. Furthermore, individuals in the 1st quintile more often were treated with lipid-lowering therapy and more often had diabetes; this was most pronounced for LDL cholesterol.

Association between Lipid Traits and Ischemic Stroke

Higher quintiles of apoB and non-HDL cholesterol were associated with increased risk of ischemic stroke with HRs of comparable magnitude, whereas for LDL cholesterol, this association was somewhat attenuated (Fig 1). Compared to individuals with apoB levels in the 1st quintile, the 2nd quintile yielded a hazard ratio (HR) of 1.07 (95% CI, 0.94–1.23), the 3rd quintile 1.16 (1.01–1.32), the 4th quintile 1.31 (1.15–1.49), and the 5th quintile 1.37 (1.20–1.56) (p for trend <0.0001). Compared to

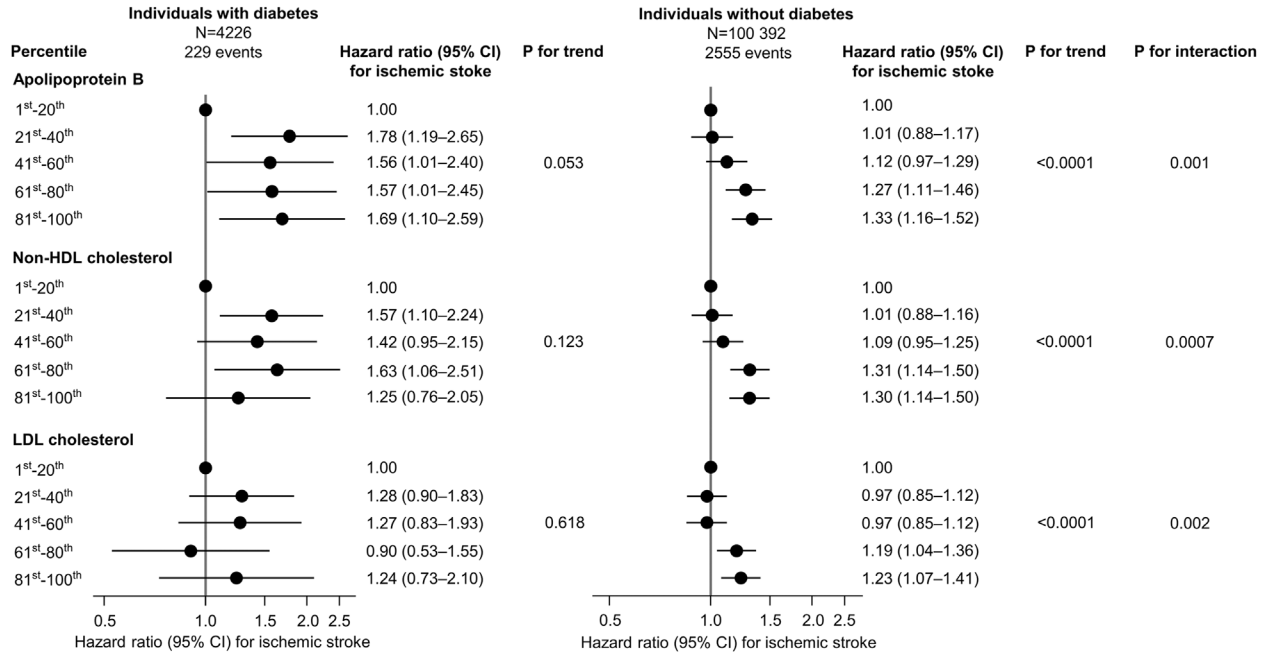

FIGURE 4: Multivariable adjusted hazard ratios for ischemic stroke according to quintiles of plasma apolipoprotein B, non-HDL cholesterol, and LDL cholesterol in individuals with and without diabetes. Analyses were adjusted for age, sex, smoking status, pack-years, alcohol intake, hypertension, lipid-lowering therapy, and atrial fibrillation. Based on individuals from the Copenhagen General Population Study. Abbreviations: CI = confidence interval; LDL = low-density lipoprotein; non-HDL = non-high-density lipoprotein.

individuals with non-HDL levels in the 1st quintile, corresponding HRs were 1.06 (95% CI, 0.93–1.21) for the 2nd quintile, 1.12 (0.98–1.27) for the 3rd quintile, 1.34 (1.18–1.52) for the 4th quintile, and 1.32 (1.16–1.50) for the 5th quintile (p for trend <0.0001). Compared to individuals with LDL cholesterol levels in the 1st quartile, corresponding HRs were 0.99 (95% CI 0.87–1.12) for the 2nd quintile, 0.98 (0.86–1.12) for the 3rd quintile, 1.17 (1.03–1.33) for the 4th quintile, and 1.22 (1.07–1.38) for the 5th quintile (p for trend 0.0005).

In addition, event rates in the 1st quintiles were lowest for apoB with 2.10 ischemic strokes per 1,000 person years, medium for non-HDL cholesterol with 2.48 ischemic strokes per 1,000 person years, and highest for LDL cholesterol with 3.00 ischemic strokes per 1,000 person years (Fig 1). Overall, the highest event rate was found in individuals with apoB in the 5th quintile.

When analyses presented in Fig 1 were done similarly for hemorrhagic stroke, neither apoB, non-HDL cholesterol, nor LDL cholesterol were associated with increased risk.

Proportion of Ischemic Strokes Attributable to Elevated Lipid Traits

PAF increased for individuals in the 2nd through to the 5th quintile of apoB and non-HDL cholesterol levels compared to individuals in the 1st quintile (Fig 2). Compared to individuals in the 1st quintile, the combined proportion of ischemic stroke attributable to apoB levels for individuals in the 2nd to 5th quintiles (>82 mg/dL) and non-HDL cholesterol levels for individuals in the 2nd to 5th quintiles (>3.0 mmol/L; >117 mg/dL) were 16.3% (95% CI, 7.9%–24.0%) and 14.7% (6.6%–22.0%), respectively. Lower PAF values were seen for individuals in the 2nd to 5th quintiles of LDL cholesterol relative to those of apoB and non-HDL cholesterol. Compared to individuals in the 1st quintile, the combined proportion of ischemic stroke attributable to LDL cholesterol levels for individuals in the 2nd to 5th quintiles (>2.4 mmol/L; >94 mg/dL) was 6.8% (−1.3%–14.2%). For these estimates, the lower value of the CI for apoB did not lap over the PAF value for LDL cholesterol, and the upper limit of the CI for LDL cholesterol did not overlap the PAF values for neither apoB nor non-HDL cholesterol.

Proportion of Ischemic Strokes Attributable to Lipid Traits in Women and Men

For sex stratification, analyses were carried out separately in 57,945 women with 1,278 ischemic stroke events and in 46,673 men with 1,506 ischemic stroke events. Analyses on women and men separately yielded similar overall results to those seen for the overall population (compare Fig 2 and Fig 3). Compared to women and men in the 1st

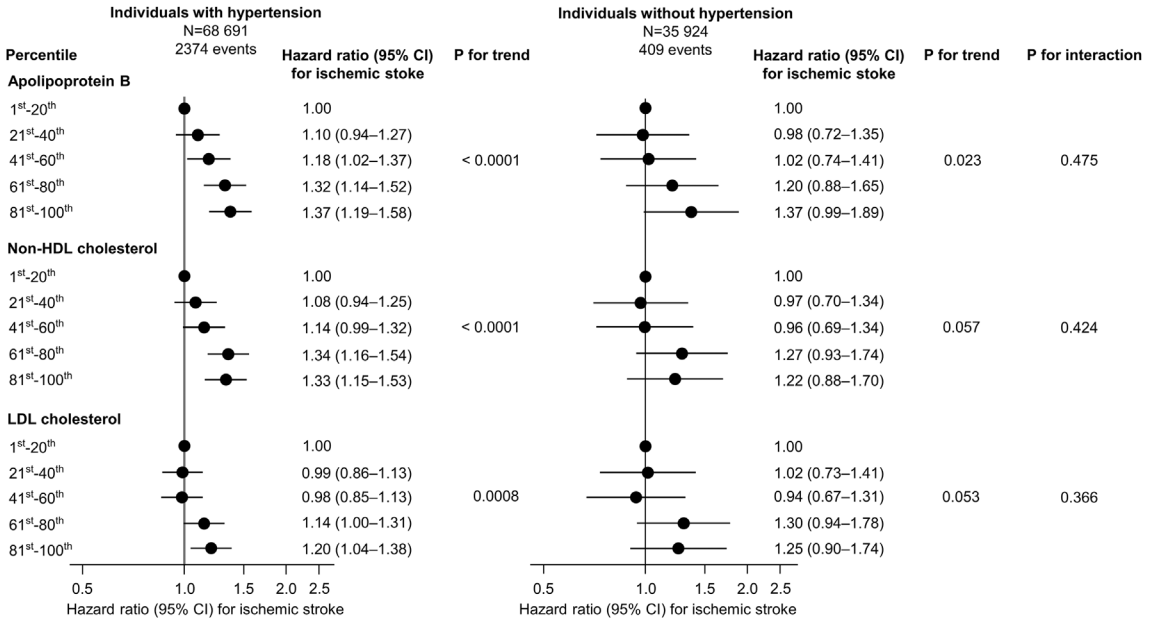

FIGURE 5: Multivariable adjusted hazard ratios for ischemic stroke according to quintiles of plasma apolipoprotein B, non-HDL cholesterol, and LDL cholesterol in individuals with and without hypertension. Analyses were adjusted for age, sex, smoking status, pack-years, alcohol intake, hypertension, lipid-lowering therapy, and atrial fibrillation. Based on individuals from the Copenhagen General Population Study. Abbreviations: CI = confidence interval; LDL = low-density lipoprotein; non-HDL = non-high-density lipoprotein.

quintile, the combined proportion of ischemic strokes attributable to apoB levels in the 2nd to 5th quintiles was 14.8% in women and 16.8% in men (Fig 3). For non-HDL cholesterol corresponding values were 15.6% in women and 12.9% in men and for LDL cholesterol 4.6% in women and 7.2% in men (Fig 3).

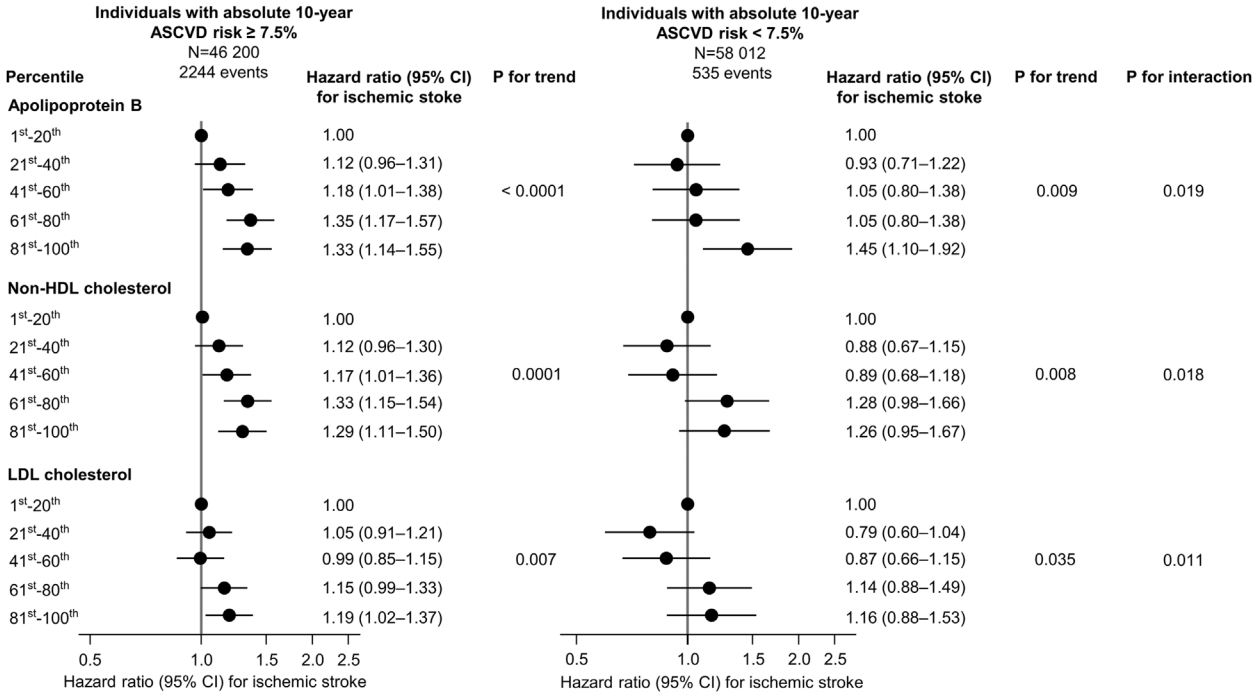

FIGURE 6: Multivariable adjusted hazard ratios for ischemic stroke according to quintiles of plasma apolipoprotein B, non-HDL cholesterol, and LDL cholesterol in individuals with absolute 10-year atherosclerotic cardiovascular disease risk <7.5% and ≥7.5%. Analyses were adjusted for age, sex, smoking status, pack-years, alcohol intake, hypertension, lipid-lowering therapy, and atrial fibrillation. Based on individuals from the Copenhagen General Population Study. Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; LDL = low-density lipoprotein; non-HDL = non-high-density lipoprotein.

Subgroups by Diabetes, Hypertension, and ASCVD Risk

HRs for ischemic stroke between lipid traits in individuals with and without diabetes, hypertension, and absolute 10-year ASCVD risk ≥7.5% are given in Figs 4–6. The statistical power in the analyses in individuals with diabetes, without hypertension, and with absolute 10-year ASCVD risk <7.5% was modest with respectively 229, 409, and 535 ischemic stroke events explaining the larger CIs around the HRs; that is, compared with individuals without diabetes, with hypertension, and with absolute 10-year ASCVD risk ≥7.5% with respectively 2,555, 2,374, and 2,244 ischemic stroke events.

In individuals with diabetes, the 2nd to 5th vs. the 1st quintiles of apoB were associated with increased risk of ischemic stroke (Fig 4). For quintiles of non-HDL cholesterol results were similar but slightly attenuated, while corresponding estimates for LDL cholesterol were further attenuated and all 95% CIs for HRs overlapped 1.0 (Fig 4). In individuals without diabetes, associations between quintiles of apoB, non-HDL cholesterol, or LDL cholesterol with risk of ischemic stroke were similar to those in the overall population (compare Figs 1–4). P for interaction between diabetes and quintiles of apoB, non-HDL cholesterol, and LDL cholesterol on risk of ischemic stroke were 0.001, 0.0007, and 0.002, respectively (Fig 4).

For individuals with and without hypertension, results were similar to those in the overall population (compare Figs 1–5). The *p* values for interaction between hypertension and quintiles of apoB, non-HDL cholesterol, and LDL cholesterol on risk of ischemic stroke were 0.475, 0.424, and 0.366, respectively (Fig 5).

For individuals with absolute 10-year ASCVD risk ≥7.5%, results were similar to those seen in the overall population (compare Figs 1–6). In individuals with absolute 10-year ASCVD risk <7.5%, only the 5th vs. the 1st quintile of apoB was significantly associated with increased risk of ischemic stroke. P for interaction between 10-year absolute ASCVD risk and quintiles of apoB, non-HDL cholesterol, and LDL cholesterol on risk of ischemic stroke were 0.019, 0.018, and 0.011, respectively (Fig 6).

For individuals with diabetes in the 2nd to 5th quintiles vs. the 1st quintile, the combined proportion of ischemic stroke attributable to apoB was 32.0%, to non-HDL cholesterol 21.8%, and to LDL cholesterol 8.5% (Fig 7). Corresponding PAF values in individuals with hypertension were 17.3% for apoB, 15.6% for non-HDL cholesterol, and 6.0% for LDL cholesterol, respectively. For individuals with ≥7.5% absolute 10-year ASCVD risk, corresponding values were 17.8% for apoB, 16.0% for non-HDL cholesterol, and 7.2% for LDL cholesterol, respectively.

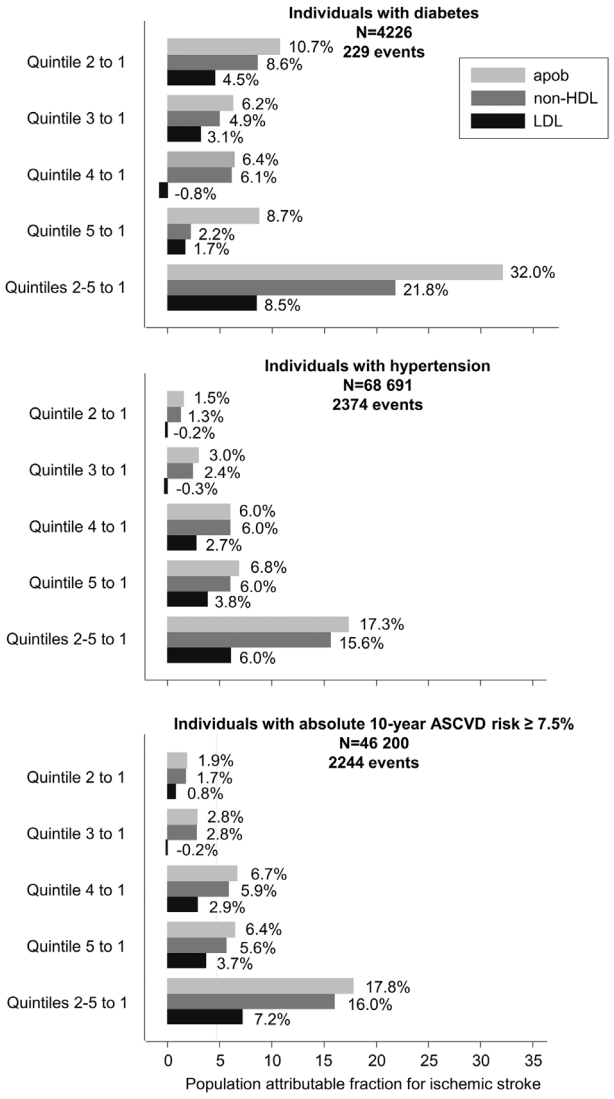

FIGURE 7: Population attributable fraction of ischemic stroke for quintiles of plasma apolipoprotein B, non-HDL cholesterol, and LDL cholesterol in individuals with diabetes, hypertension, or absolute 10-year atherosclerotic cardiovascular disease risk ≥7.5%. Calculations by Miettinen's formula were based on multivariable adjusted hazard ratios. Analyses were adjusted for age, sex, smoking status, pack-years, alcohol intake, hypertension, lipid-lowering therapy, and atrial fibrillation. Estimated absolute 10-year atherosclerotic cardiovascular disease risk was based on the Pooled Cohort Equations. Based on individuals from the Copenhagen General Population Study. Abbreviations: LDL = low-density lipoprotein; non-HDL = non-high-density lipoprotein.

Discussion

This study of 104,618 individuals from the Copenhagen General Population Study found that higher quintiles of apoB and non-HDL cholesterol were associated with

increased risk of ischemic stroke, while for LDL cholesterol this association was somewhat attenuated. Indeed, the proportion of ischemic stroke attributable to either elevated apoB or non-HDL cholesterol was double the proportion attributable to elevated LDL cholesterol. This novel finding indicates that risk of ischemic stroke is better reflected by elevated levels of apoB and non-HDL cholesterol than by elevated levels of LDL cholesterol.

A likely explanation is that atherosclerosis plays an overall substantial role in the development of ischemic stroke and that cholesterol of all apoB-containing particles, not only that in LDL particles, is atherogenic. Previous studies showing an association of elevated triglycerides or remnant cholesterol with increased risk of ischemic stroke supports this explanation[10,11,30,31] as elevated non-HDL cholesterol and apoB include, in addition to LDL particles, elevated triglyceride-rich remnant lipoproteins. Triglyceride-rich remnant particles have high triglyceride content and contain remnant cholesterol; thus, elevated levels of these lipoproteins are marked by elevated triglycerides and elevated remnant cholesterol. However, ischemic stroke is a heterogenous disorder with a variety of etiologies and pathologies; therefore, other mechanistic explanations for our findings also should be considered.

Previous studies found conflicting results, although most studies reporting no significant association of elevated LDL cholesterol, non-HDL cholesterol, or apoB with risk of ischemic stroke found risk estimates in the expected direction of higher risk.[13–19] These nonsignificant findings could be due to power issues; however, another explanation might be heterogeneity of ischemic stroke disorders, as atherosclerosis may not be part of the pathogenesis of all subtypes. In that case, including non-atherosclerotic ischemic stroke in the outcome could result in dilution of a possible major association between atherosclerotic lipids and increased risk of atherosclerotic ischemic stroke. A third explanation may be that strokes often occur at older ages than ischemic heart disease; thus, in studies originally designed to examine ischemic heart diseases, participants might be too young to find significant associations on stroke outcomes. However, our study had the power to detect associations of elevated lipid traits with increased risk of ischemic stroke despite ischemic strokes occurring at a median age of 69 years.

For risk of ischemic stroke in men and women separately, diverging results have previously been reported for elevated LDL cholesterol, non-HDL cholesterol, or apoB. For example, the women's health study consistently found that non-HDL cholesterol was associated with increased risk of ischemic stroke in women.[7,14] However, LDL cholesterol was associated with increased risk of ischemic stroke in one study[7] but not in the other.[14] Also, in a cohort of middle-aged men, no association between plasma lipid parameters and risk of ischemic stroke was found.[17] Nevertheless, a previous smaller study on the Danish general population found a stepwise increased risk of ischemic stroke across apoB tertiles in both sexes and an insignificant similar stepwise association for LDL cholesterol and non-HDL cholesterol in women, but not in men.[16] Furthermore, no significant associations of elevated LDL cholesterol or apoB with risk of ischemic stroke were found in men or women in the ARIC study. Finally, a large cohort study in China found no significant sex interaction for the association between elevated LDL cholesterol and risk of ischemic stroke.[11,13] The current study found that the proportion of ischemic stroke attributable to LDL cholesterol, non-HDL cholesterol, and apoB quintiles across sexes resembled the pattern for the overall population that is, risk of ischemic stroke appears to be better reflected by elevated levels of apoB and non-HDL cholesterol than by elevated levels of LDL cholesterol. To our knowledge, our study is the largest to date to examine this association in women and men separately.

In the present study, PAF values for apoB and non-HDL cholesterol in individuals with diabetes were higher than for the overall population. Of note, lipid levels in this subgroup are, in general, lower compared to lipid levels in the overall population; hence, a larger proportion of these individuals are within the lower quintiles. This is possibly because a larger proportion of individuals with diabetes is treated with lipid-lowering therapy than in the overall population and because the dyslipidemia in diabetes typically is characterized by elevated triglycerides, elevated remnant cholesterol, and low to average LDL cholesterol. Even though there are relatively more ischemic stroke events among individuals with diabetes than in the overall population, one could think that the number of ischemic strokes that occur in this subgroup is lower than expected as statins have been shown to reduce the risk of stroke.[20–22] Therefore, comparison of PAF values between individuals with diabetes and the overall population needs to be considered with caution.

Strengths of the present study include the large statistical power of our cohort in terms of the large number of individuals recruited, long-term follow-up, and the ability to adjust for many confounders. In addition, despite ischemic stroke occurring at a median age of 69 years, we had power to detect associations. Finally, due to complete Danish health registries, we were able to follow all individuals from baseline with no loses to follow-up.

Limitations of our study include restrictions regarding generalization of our results across ethnicities because this study included white individuals only. Therefore, we cannot determine whether these results would hold up in

populations of non-white ethnicity. That said, we are not aware of data to suggest that our results would not apply to people of other ethnicities. Nevertheless, an international case–control study from 2016 found variations in the importance of individual risk factors for stroke across region and ethnicity.[32] Also, information on changes in type and dose of lipid-lowering therapy was not available during follow-up in our study; thus, we cannot exclude that our results could have been influenced by individuals starting or stopping their lipid-lowering treatment after the baseline examination. Furthermore, because our registers are limited to ischemic and hemorrhagic stroke, we were not able to analyze subtypes as embolic stroke or large vessel vs. small vessel stroke. In addition, we used single imputation of missing data; however, given the small amount of missing data, the results were similar in analyses using multiple imputation and when patients with missing data were excluded. Finally, our study was observational and, therefore, cannot deal with questions regarding causality to explore the differences in etiology and pathology of subtypes of ischemic stroke.

Clinically, ischemic stroke is an important cause of long-term disability, dementia, and depression[3]; hence, improvement of preventive strategies would be of great value to both individuals, healthcare systems, and societies. The present study indicates that elevated apoB and non-HDL cholesterol are better markers of risk of ischemic stroke than elevated LDL cholesterol. Whether focus on lowering of apoB or non-HDL cholesterol rather than LDL cholesterol could improve preventive strategies needs to be examined in future studies.

Conclusions

The burden of ischemic stroke attributable to elevated apoB and non-HDL cholesterol is double that attributable to elevated LDL cholesterol. This suggest that assessment of apoB and non-HDL cholesterol should be preferred over the traditional assessment of LDL cholesterol solely when estimating risk of ischemic stroke.

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Author Contributions

C.D.L.J., M.B.M., A.L., B.G.N. contributed to the conception and design of the study; C.D.L.J., M.B.M., A.L., B.G.N. contributed to the acquisition and analysis of data; C.D.L.J. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

Nothing to report.

Data Availability

Upon reasonable request, additional analyses can be performed after contact to the corresponding author.

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