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# Lipid Levels During Adult Lifetime in Men and Women With and Without a Subsequent Incident Myocardial Infarction: A Longitudinal Analysis of Data From the Tromsø Study 1974 to 2016

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**BACKGROUND:** The atherosclerotic effect of an adverse lipid profile is assumed to accumulate throughout life, leading to increased risk of myocardial infarction (MI). Still, little is known about age at onset and duration of unfavorable lipid levels before MI.

**METHODS AND RESULTS:** Longitudinal data on serum lipid levels for 26 130 individuals (50.5% women, aged 20–89 years) were obtained from 7 population-based health surveys in Tromsø, Norway. Diagnoses of MI were obtained from national registers. A linear mixed model was applied to compare age- and sex-specific mean values of total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride concentration by MI status (MI versus non-MI). Already from young adulthood, 20 to 35 years before the incident MI, individuals with a subsequent incident MI had on average more adverse lipid levels than individuals of the same age and sex without MI. Analogous to a dose–response relationship, there was a clear trend toward more severe adverse lipid levels the lower the age at incident MI ($P<0.001$, test for trend through ordered categories <55, 55–74, ≥75 years). This trend was particularly pronounced for high-density lipoprotein cholesterol in percentage of total cholesterol (both sexes) and for the relative relationship between triglyceride, high-density lipoprotein cholesterol, and total cholesterol level (women). The difference in mean lipid level by MI status was just as large in women as in men, but the age pattern differed ($P\leq0.05$, tests of 3-way interaction).

**CONCLUSIONS:** Compared with general population mean levels, adverse lipid levels were seen 20 to 35 years before the incident MI in both men and women.

**Key Words:** incident myocardial infarction ■ lipid profile ■ longitudinal study

A poor lipid profile is a major risk factor for coronary heart disease (CHD), and the atherosclerotic promoting effect of an adverse lipid profile is assumed to accumulate over time before an increased risk is established.[1–3] A lower age at onset of unfavorable lipid levels in men than in women,[4,5] possibly in combination with other unfavorable lipoprotein characteristics in men,[6] may thus contribute to the 10-year sex difference in mean age at the incident MI.[7] Moreover, a longer duration of unfavorable lipid levels may contribute to the

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## CLINICAL PERSPECTIVE

### What Is New?

- Longitudinal data on adult lifetime lipid levels from the Tromsø Study 1974 to 2016 revealed a period of 20 to 35 years with unfavorable lipid levels in individuals with a subsequent incident myocardial infarction (MI).
- Adverse lipid levels occurred at an earlier age in individuals with MI <74 years than ≥75 years, and there was a clear trend toward more severe adverse lipid levels the lower the age at the incident MI.
- The maximum difference in mean lipid levels between individuals with and without MI was equally large among women as men but appeared later in life in women.

### What Are the Clinical Implications?

- Results from this study point to a need for awareness of adverse lipid levels at all ages throughout adult lifetime.
- Intervention strategies targeting improved lipid profiles at ages when awareness of MI is still low may have a substantial impact on subsequent risk of MI.

estimated overall higher risk of CHD in men in ordinary analyses adjusted for age and traditional risk factors, including the level of, but not the duration of, adverse lipid levels.[8] However, the empirical evidence to support the hypothesis involving an accumulated effect of unfavorable lipid levels is limited because most prospective, population-based studies have risk factor information gathered from a single time point. Even with access to longitudinal data, it is difficult to quantify age at the first exposure and duration of adverse exposure before an incident MI. The normal range of lipid levels may also change with increasing age.[9,10]

Different analytic strategies have been applied to examine the time-related exposure to risk factors of cardiovascular diseases (CVDs).[11] A common strategy in the few previous studies that examined the effects of lipid levels during lifetime has been to compare the risk of CHD or CVD between groups defined by the shape of lipid trajectories over a certain period of life, with risk group membership identified by means of latent class model analyses or alternative analytic techniques.[12,13] This approach is most often applied to identify high-risk groups that share a certain risk factor profile.[14] A recent study[15] used the area under such model-based lipid trajectory curves as a summary measure of long-term burden of an adverse lipid profile during ages 20 to 58 years in relation to subsequent risk of CVD. The authors concluded that both the shape of lipid trajectories and the total amount of exposure to adverse lipid levels in young adulthood have a significant impact. Another recent study using the same summary measure of long-term exposure[16] found that accumulated exposure to low-density lipoprotein cholesterol (LDL-C) during ages 20 to 30 years, as compared with ages 30 to 42 years, was associated with a greater increase in the risk of CVD events. The association was mainly seen in men. In both studies, the follow-up on CVD events was limited to ages ≤60 years. Still another study[17] reported that high LDL-C levels during young adulthood, represented by the average of repeated LDL-C measurements, were associated with an increased risk of CVD events independent of midlife LDL-C level. Thus, age at exposure appears to play a role in the adverse effects of unfavorable lipid levels, but little is known about the duration of adverse lipid levels before a harmful effect occurs, or whether there are any sex differences in any of these time aspects.

An alternative analytic approach for examining the effects of long-term exposure to unfavorable lipid levels, with a focus on both age at onset and duration of exposure, is to examine whether lipid levels during the lifetime of individuals who develop CHD deviate from patterns related to normal aging in the general population. Age- and sex-specific lipid levels in the general population during a lifetime have been reported in a few longitudinal studies[18–20] and some cross-sectional and register-based studies,[9,10,21,22] but we are not aware of any studies that have compared lifetime lipid-level trajectories in the general population with patterns in individuals who later in life develop CHD.

The aim of the present study was to explore the hypothesis of an adverse effect of long-term exposure to unfavorable lipid levels by performing a direct comparison of mean lipid levels at different ages during adulthood between individuals with and without a subsequent diagnosis of incident myocardial infarction (MI). Potential sex differences in this contrast were also examined. Moreover, analyses according to age at diagnosis of MI were performed to explore the length of a potential latency time related to prolonged adverse lipid levels. The results from this study are based on longitudinal data on lipid levels at ages 20 to 89 years from 7 population-based health surveys in the Tromsø Study, Norway, with diagnoses of MI obtained from local and national registers. Study participants without a diagnosed MI were considered representative of the general population.

## METHODS

### Data Availability Statement

The present study used data on lipid measurements from the Tromsø Study, linked to data on MI from

regional and national disease registers in Norway. The data file generated and analyzed during the current study are not publicly available due to Norway's laws related to privacy of health data. Details on how to get access to data from the Tromsø Study are given elsewhere (https://helsedata.no/no/forvaltere/universitetet-i-tromso/tromsoundersokelsen/). The analytic methods applied are described in detail within the article (Statistical Analysis) and in Data S1. Program codes (SPSS) and additional details on the analytical methods applied can be provided upon reasonable request to the corresponding author.

## Study Population

The Tromsø Study is an ongoing population-based cohort study in the municipality of Tromsø, northern Norway, with a population of 78 000 inhabitants (46 000 in 1979). The study includes data on serum lipid levels from 7 health surveys carried out at regular time intervals (mean time interval between 2 subsequent surveys in the range, 5.3–8.1 years) in the period 1974 to 2016.[23] Both total birth cohorts and representative samples of the population (new and former participants) were invited to each survey (response proportion, 65%–79%). The first 3 surveys comprised individuals aged 20 to 49 years (men only), 20 to 54 years (20–49 years for women) and 20 to 61 years (20–56 years for women), respectively, whereas the last 4 surveys included individuals aged 30 to 97 years. The third survey also included a subsample of young adults (<20 years). So far, the Tromsø Study has included a total of 45 473 individuals.

The present study population comprises 26 130 individuals (50.5% women) with at least 2 Tromsø survey participations before an incident MI or closing date of study in December 2019. Data from the Tromsø Study were linked to information on MI from regional and national disease registers (date on diagnosis in the period 1974–2019) by means of the unique Norwegian 11-digit personal identification numbers. Of the 26 130 study participants, a total of 32%, 24%, 19%, 14%, and 11% had participated in 2, 3, 4, 5, and 6 to 7 surveys, respectively. Only data from survey participations at ages 20 to 89 years were included because there was a limited number of study participants outside this age range. Data from survey participations after an incident MI were not considered. The median age at first survey participation in our study population was 31 years for men (interquartile range, 26–39) and 32 years for women (interquartile range, 27–41 years), whereas the median time interval between the first and last survey participation considered in the present study was 21 (range, 4–42) years in men and 21 (range, 5–37) years in women.

The present study was approved by the Regional Committee for Medical and Health Research Ethics and the Data and Publication Board of the Tromsø Study. The Tromsø Study has previously been approved by the Norwegian Data Inspectorate and the Regional Committee for Medical and Health Research Ethics. Written informed consent for using data from the Tromsø Study in future research projects was introduced in 1994 (fourth and later surveys), and additional written informed consent for use of data in the present study is thus not required. In case of withdrawal of consent, data are deleted in the original database.

## Incident MI

Date of diagnosis of MI in the period 1974 to 2014 was obtained from the Tromsø Study Cardiovascular Disease Register (*International Classification of Diseases, Eighth Revision* [*ICD8*], *Ninth Revision* [*ICD9*], and *Tenth Revision* [*ICD10*] codes), whereas diagnoses in the period 2015 to 2019 were obtained from the Norwegian Myocardial Infarction Register (*ICD-10* code I21 or I22). The national Cause of Death Registry provided data on out-of-hospital fatal incident cases of MI (*ICD-10* code I21-I22). Deaths registered with ischemic heart disease as an underlying or contributing cause of death (*ICD-10* codes I20 and I23-25) were also defined as incident MI. The diagnoses recorded in the national register for the period 2013 to 2014 have been found to be highly correct and complete, as compared with the validated diagnoses in the regional register.[24]

Of the 26 130 individuals included in the present study, a total of 2714 (1966 men, 748 women) were diagnosed with incident MI at ages 35 to 97 years. The median time interval between the last survey participation and the date of diagnosis of MI in the subgroup with MI was 4.3 years (interquartile range, 1.9–8.3) in men and 4.4 years (interquartile range, 1.7–8.4) in women.

## Serum Lipid Measurements

At each Tromsø Study survey, nonfasting concentrations of serum total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured by standard methods using commercial kits. Individual data on lipid measurements used in the present study covered the age interval defined by the date of the first survey participation and the date of the last participation before the diagnosis of MI (MI group) or closing date of study in December 2019 (non-MI group). An additional measure of total cholesterol and HDL-C at the time of the diagnosis was available from the Norwegian Myocardial Infarction Register. These values were used for 209 individuals (140 men, 69 women) who were diagnosed with MI in the period 2013 to 2019 but lacked complete data from the seventh Tromsø Study in 2015 to 2016.

Table 1 shows the total number of study participants by age at the survey participation (5-year categories) in men and women with and without a subsequent incident MI. HDL-C was not registered in the first survey, and triglyceride was not measured at the date of MI. Thus, the number of total cholesterol measurements (91 584 observations, 0.3% missing values) was somewhat higher than the total number of available triglyceride and HDL-C measurements (91 362 and 86 077 observations, respectively).

## Statistical Analysis

The sample mean values of the different lipid variables are presented with 95% CIs in subgroups defined by age at serum lipid measurement (5-year categories), sex, and MI status at the closing date of the study in December 2019 (MI and non-MI, respectively). Pearson and Spearman correlation coefficients, based on data from all time points, were used to examine the relation between triglyceride and cholesterol levels.

A linear mixed model was applied to estimate the mean serum lipid trajectories during a lifetime. Subject (individual) was defined as a random-effect factor, whereas age at the serum lipid measurement (1-year intervals), sex (men, women), and MI status at the closing date of the study (MI, non-MI) were included as fixed-effect factors. Alternative regression models were evaluated to fit the observed nonlinear age trajectories, but a cubic polynomial (with a linear, quadratic, and cubic term) gave best fit to data, both in terms of distance between observed and predicted mean values (visual check) and lowest Akaike information criterion value. A full factorial 3-way interaction model (Data S1) was applied to allow for heterogeneity in adult lifetime lipid trajectories in the 4 subgroups defined by sex and MI status. Accordingly, the model allowed for age- and sex-specific differences in mean lipid level by MI status. An unstructured variance/covariance matrix was applied to take account of the inherent dependency in individual data on lipid measurements (model with lowest Akaike information criterion). Statistical tests on heterogeneity in age trajectories by MI status (2-way interaction models, Data S1) were carried out in sex-specific analyses.

To provide more detailed information on duration of adverse lipid levels before the incident MI, additional analyses with the MI group further categorized by age at diagnosis (<55, 55–74, and ≥75 years) were performed. The formal statistical analyses, including test for trend in mean lipid levels through the ordered categories of age at the incident MI, were restricted to lipid measurements in the age interval 35 to 49 years to ensure that data in all groups were compared. The age trajectories in this limited age interval were modeled as a linear trend rather than a cubic polynomial

**Table 1. Number of Men and Women With and Without a Subsequent Incident MI (MI and Non-MI, respectively) by Age at Survey Participation*: The Tromsø Study 1974 to 2016**

| | | | No. of observations by age (5-y categories) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. of individ† | No. of observ‡ | 20– | 25– | 30– | 35– | 40– | 45– | 50– | 55– | 60– | 65– | 70– | 75– | 80– | 85– |
| Men, non-MI | 10957 | 39 767 | 2247 | 3815 | 4485 | 4475 | 4962 | 4521 | 3847 | 2888 | 3277 | 2481 | 1567 | 792 | 332 | 78 |
| Women, non-MI | 12459 | 42899 | 1929 | 3613 | 4599 | 4461 | 5321 | 4771 | 3967 | 3679 | 3778 | 2956 | 2025 | 1130 | 515 | 155 |
| Men, MI | 1966 | 6767 | 194 | 358 | 617 | 800 | 956 | 1031 | 846 | 551 | 506 | 402 | 279 | 175 | 61 | 21 |
| MI <55y | 458 | | 102 | 156 | 216 | 251 | 229 | 165 | 71 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| MI 55–74y | 1138 | | 92 | 202 | 379 | 478 | 591 | 655 | 584 | 408 | 342 | 221 | 69 | 0 | 0 | 0 |
| MI ≥75y | 370 | | 0 | 0 | 22 | 71 | 136 | 211 | 191 | 143 | 164 | 181 | 210 | 175 | 61 | 21 |
| Women, MI | 748 | 2432 | 18 | 54 | 101 | 158 | 257 | 321 | 225 | 254 | 257 | 258 | 266 | 158 | 79 | 26 |
| MI <55y | 54 | | 11 | 21 | 28 | 28 | 27 | 23 | 9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| MI 55–74y | 370 | | 7 | 33 | 73 | 122 | 183 | 214 | 153 | 177 | 161 | 69 | 49 | 0 | 0 | 0 |
| MI ≥75y | 324 | | 0 | 0 | 0 | 8 | 47 | 84 | 63 | 77 | 96 | 189 | 217 | 158 | 79 | 26 |
| Total no. | 26 130 | 91 895 | 4388 | 7840 | 9802 | 9894 | 11 496 | 10644 | 8885 | 7372 | 7818 | 6097 | 4137 | 2255 | 987 | 280 |

MI indicates myocardial infarction.
*The study population comprises individuals who participated in at least 2 of 7 surveys during ages 20 to 89 years before incident MI or end of follow-up with respect to diagnosis of MI in December 2019 (closing date of study).
†Number of study participants with ≥2 survey participations.
‡Number of lipid measurements, total and by age at survey participations (5-year categories).

(no-interaction model), and the analyses were performed separately for men and women.

Maximum-likelihood estimates of regression coefficients were calculated by means of the linear mixed module in SPSS.[25] The full-factorial 3-way interaction model (Data S1) was used to compute the model-based predicted mean age trajectories for each lipid variable in the 4 subgroups defined by sex and MI status. The corresponding estimated age- and sex-specific regression coefficients for MI status (MI versus non-MI) are presented together with 95% CI and *P* values from likelihood ratio tests. The CIs were obtained through repeated analyses with successive changes in the reference values for age and sex (recoding of variables). The analyses of triglyceride levels were based on log-transformed data due to a skew distribution. The estimated regression coefficients were back-transformed to reflect relative difference in mean triglyceride level on the original scale (recalculated into percentage).

## RESULTS

Men had in general a more adverse lipid profile than women, with markedly lower mean HDL-C levels throughout life and higher total cholesterol and triglyceride levels, especially before the age of 55 to 60 years (Figure 1A through 1F). In both sexes, the serum triglyceride concentration correlated more strongly with HDL-C in proportion of total cholesterol than with each cholesterol variable alone (Table S1). A nonlinear negative association was seen, with persistently low triglyceride levels when ≥40% of the total cholesterol level was HDL-C (Figure S1). In more men than women, however, high triglyceride levels occurred despite a high proportion of HDL-C, although this group was very small. In view of the observed intercorrelation, we also analyzed the ratio between triglyceride level and HDL-C in proportion of total cholesterol, in addition to the simple ratio between triglyceride concentration and HDL-C. The age patterns in individuals without MI are now described before focusing on the contrasts by MI status.

### Lipid Level Trajectories in Men and Women Without MI

In our general population cohort, the mean total cholesterol level was about 5 mmol/L in both sexes at ages 20 to 24 years (Figure 1A). In men, the total cholesterol level increased rapidly with age, reached a maximum slightly above 6 mmol/L at ages 45 to 49 years, and then decreased. A less steep age-related increase was seen in women, and the maximum value around 6 mmol/L was reached at a higher age (55–59 years). The mean level remained at this level throughout life, and consequently, the total cholesterol level was higher in women than men after the age of about 55 years.

The HDL-C levels increased slowly with age in both sexes, from 1.6 mmol/L to slightly above 1.7 mmol/L in women, and from about 1.3 to almost 1.5 mmol/L in men (Figure 1B). The age curves for HDL-C in percentage of the total cholesterol level were approximately U-shaped, especially in men (Figure 1C). The mean value of this lipid ratio was higher in women than men throughout life (27%–32% versus 23%–28%), though similar at ages ≤65 years. The lowest proportion of HDL-C, and thus the highest proportion of non–HDL-C, was seen during ages 40 to 49 years in men (24%) and at ages 55 to 59 years in women (27.5%).

The mean triglyceride concentration increased rapidly with age in men, from 1.4 mmol/L at ages 20 to 24 years to nearly 1.8 mmol/L at ages 45 to 49 years and subsequently decreased (Figure 1D). In contrast, women had invariably low mean triglyceride values (≤1.0 mmol/L) until the age of about 40 years, followed by an increase up to a maximum around 1.5 mmol/L from the age of about 60 years (Figure 1D). The age trajectories for the 2 ratios involving triglycerides were similar in shape to those for triglyceride alone (Figure 1E and 1F). The ratio between the triglyceride and HDL-C level (Figure 1E) remained higher for men than women throughout life (range, 1.2–1.5 versus 0.8–1.0), with a considerably more pronounced sex difference before than after the age of 60 years. The mean value of the ratio between triglyceride level and the proportion of HDL-C (Figure 1F) was also considerably higher in men than women before the age of 60 years (range, 6–9 versus 4–6), but no notable sex difference was seen at higher ages (mean value close to 6 in both sexes).

### Age- and Sex-Specific Differences in Mean Lipid Levels by MI Status

The estimated age trajectory curves (Figures 2 and 3) fitted the empirical data (Figure 1) well, though with a poorer prediction among the youngest and oldest. A lower sample size (Table 1) contributed to imprecise estimates at these ages. The estimated age- and sex-specific differences in mean lipid level by MI status (with 95% CI) are presented in Table 2, with a graphical display in Figures 2 and 3 (right column).

Already from ages 25 to 30 years, individuals with a subsequent incident MI had on average higher mean total cholesterol and triglyceride levels and lower HDL-C levels than individuals at the same age without a subsequent incident MI (Table 2, Figures 2 and 3). The magnitude of absolute differences varied significantly by age for all cholesterol variables in men ($P<0.001$, test of 2-way interaction; Table 3) and for all lipid variables in women ($P\leq0.011$, test of 2-way interaction; Table 3). Notably, the contrast in mean lipid level by MI status was equally large in women as in men (Table 2, Figure 2 and 3), but the age pattern differed

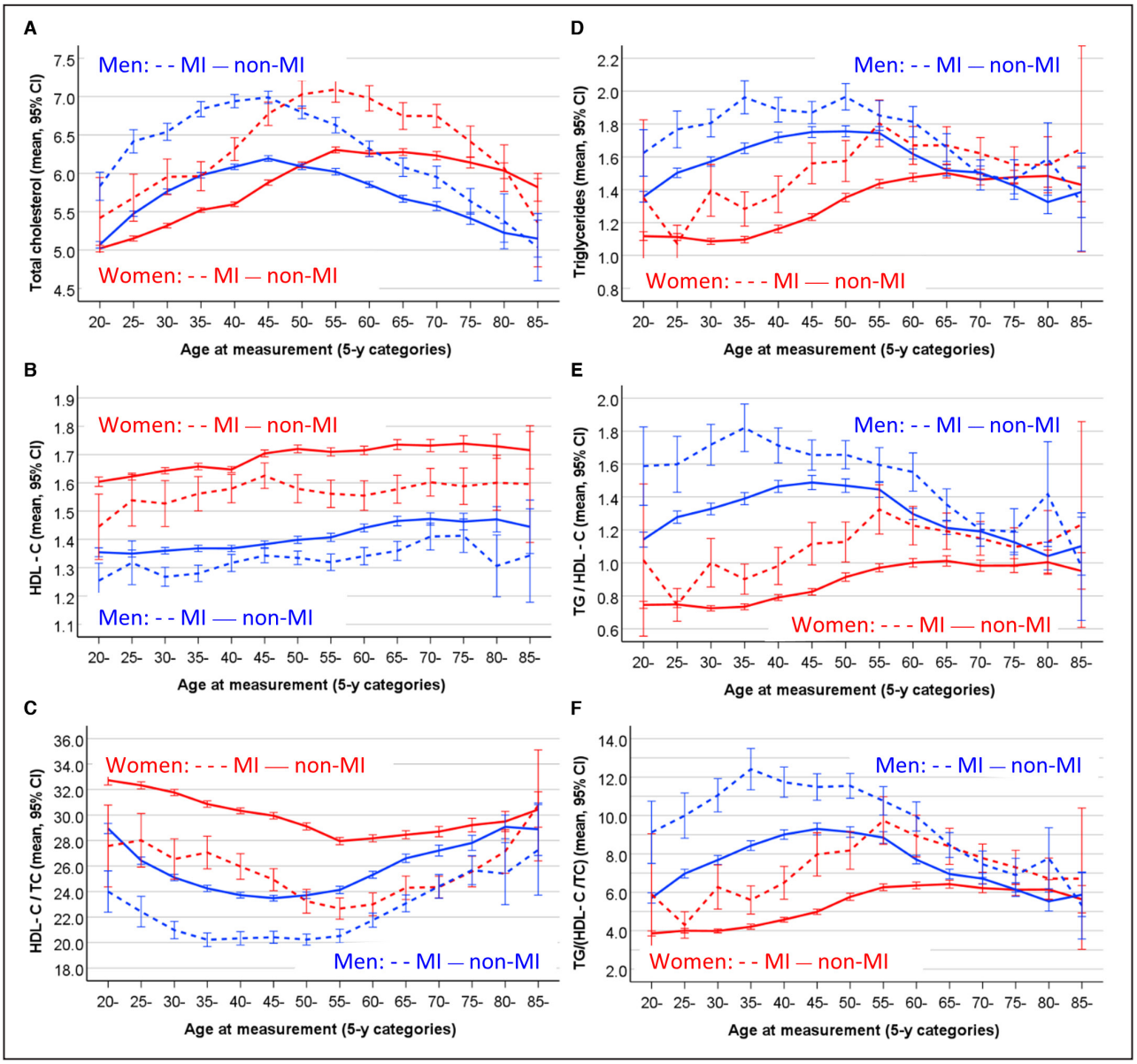


**Figure 1. Mean lipid levels by age, sex, and MI status: The Tromsø Study 1974 to 2016.**
Sample mean values with 95% CI of (**A**) TC (mmol/L), (**B**) HDL-C (mmol/L), (**C**) HDL-C in percentage of TC (HDL-C/TC, %), (**D**) TG (mmol/L), (**E**) the ratio between TG and HDL-C (TG/HDL-C), and (**F**) the ratio between TG and HDL-C in proportion of TC (TG/[HDL-C/TC]) during the adult lifetime in men and women with and without a subsequent incident MI (MI and non-MI, respectively). HDL–C indicates high-density lipoprotein cholesterol; MI, myocardial infarction; TC, total cholesterol; and TG, triglyceride.

significantly ($P \leq 0.05$, test of 3-way interaction; Table 3), except for a borderline significant difference for serum triglyceride concentration ($P=0.075$).

In general, the largest differences in mean lipid levels by MI status were seen later in life in women than in men, coinciding with the ages when the population mean values were at their extremes (Figures 2 and 3). The maximum difference in mean total cholesterol levels by MI status was nearly 1 mmol/L for both sexes (Table 2, Figure 2A). The contrast in HDL-C level by MI status increased slightly with age in both sexes (Table 2, Figure 2B) but even the largest difference was moderate (0.1–0.2 mmol/L). In contrast, HDL-C in proportion of total cholesterol (in percentage) was markedly lower throughout adult lifetime in individuals with versus without a subsequent incident MI, with a maximum difference of 5 to 6 percentage points (Table 2, Figure 2C). The triglyceride levels also differed markedly by MI status, apparently even more for women than men (18%–19% versus 11%–12%; Table 2). However, the mean values in the reference population were considerably lower in women than men (Figure 3A). The age pattern as well as the contrast by MI status in the mean value of the 2 lipid ratios involving triglycerides

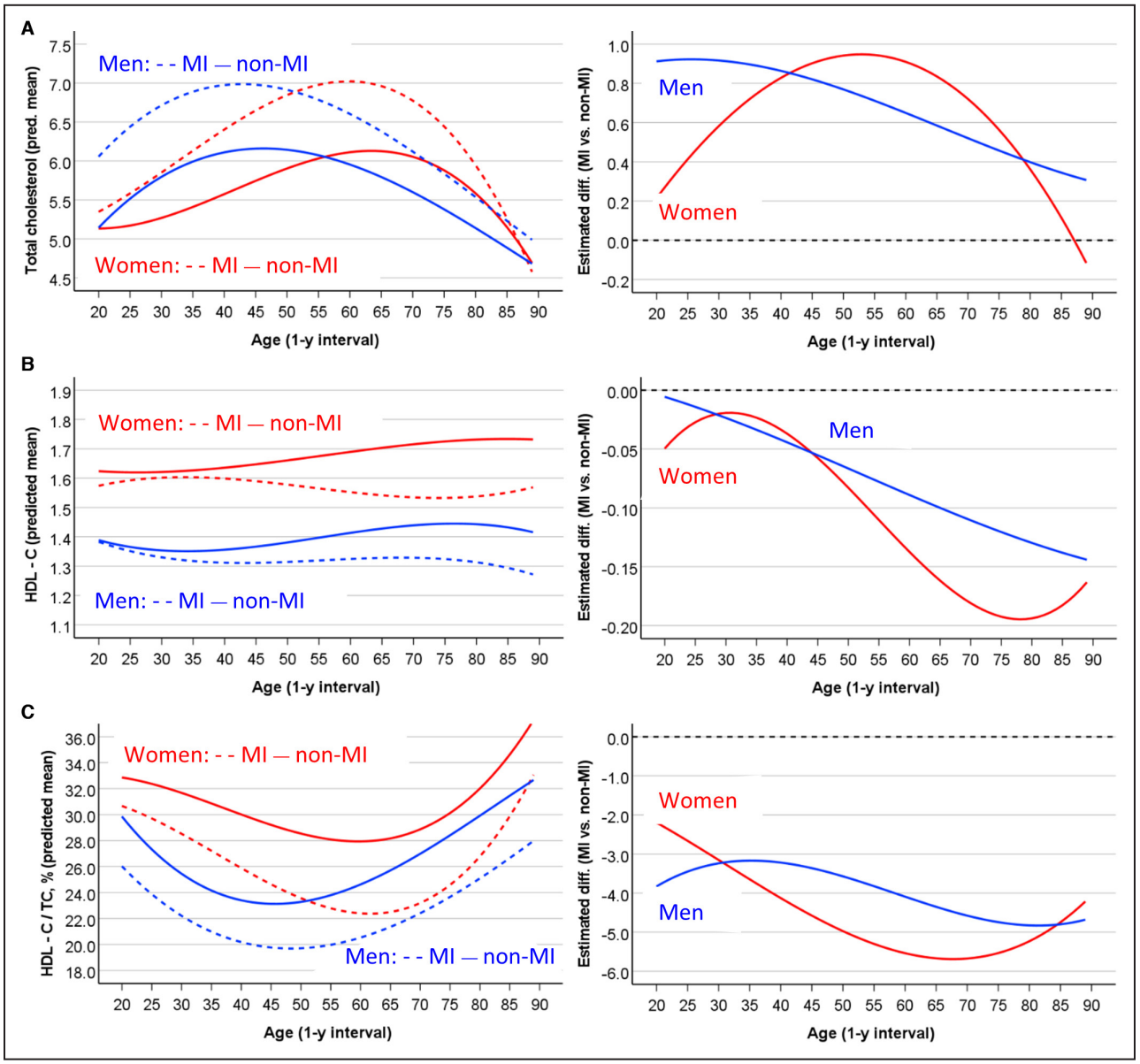


**Figure 2. Predicted mean lipid-level trajectories and the estimated age- and sex-specific differences in mean lipid levels by MI status: The Tromsø Study 1974 to 2016.**
Model-based age- and sex-specific predicted mean values (left column) of (**A**) TC (mmol/L), (**B**) HDL-C (mmol/L), and (**C**) HDL-C in percentage of TC (HDL-C/TC, %) in individuals with and without a subsequent incident MI (MI and non-MI, respectively), and the estimated age-specific differences in mean lipid levels by MI status (MI vs non-MI) in men and women (right column). HDL–C indicates high-density lipoprotein cholesterol; MI, myocardial infarction; and TC, total cholesterol.

(Table 2, Figures 3B and 3C) approximated the one for the triglycerides, but the contrast by MI status appeared to be even more pronounced. However, a direct comparison of the magnitude of difference by MI status is difficult due to the different unit of measurements. For all triglyceride variables, the contrast by MI status was constant across age in men, whereas a transient increase was seen in women due to a more pronounced increase in levels during ages 25 to 55 years in individuals with a subsequent MI.

Despite the age-related differences in the contrast by MI status in most lipid variables considered, a general impression was that the age curves for individuals with and without MI were roughly parallel, though with a markedly poorer lipid profile among individuals with a subsequent incident MI (Figure 1). A further categorization by age at diagnosis is needed to explore the duration of adverse lipid levels before an incident MI.

## Age at Onset, Severity, and Duration of Adverse Lipid Levels Before Incident MI

Among individuals diagnosed with MI at an age <55 years and 55 to 74 years, respectively, the mean

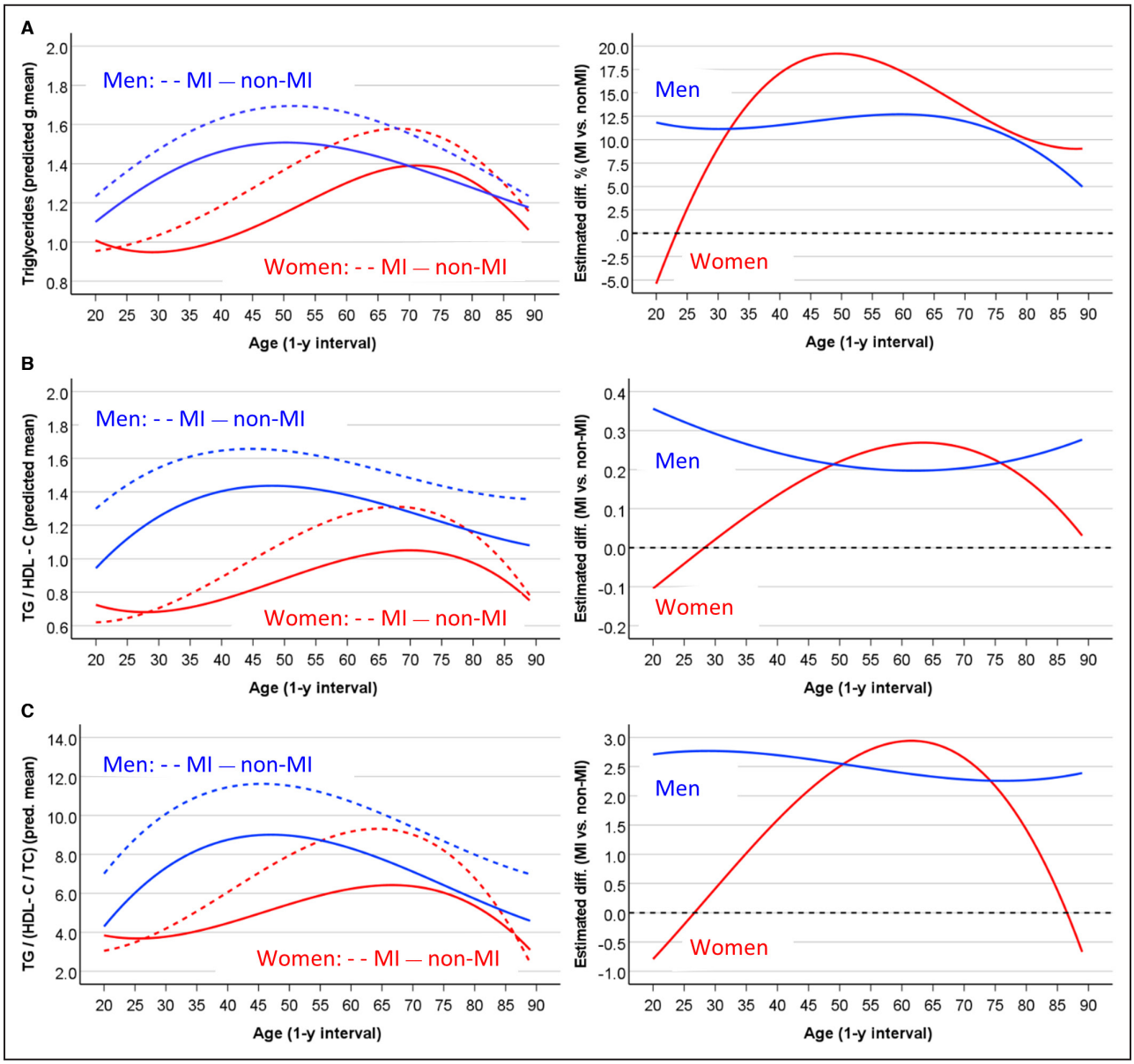


**Figure 3. Predicted mean lipid-level trajectories and the estimated age- and sex-specific differences in mean lipid levels by MI status: The Tromsø Study 1974 to 2016.**

Model-based age- and sex-specific predicted mean values (left column) of (**A**) TG (mmol/L), (**B**) the ratio between TG and HDL–C (TG/HDL-C), and (**C**) the ratio between TG and HDL-C in proportion of TC (TG/[HDL-C/TC]) in individuals with and without a subsequent incident MI (MI and non-MI, respectively), and the estimated age-specific differences in mean lipid levels by MI status (MI vs non-MI) in men and women (right column). HDL–C indicates high-density lipoprotein cholesterol; MI, myocardial infarction; TC, total cholesterol; and TG, triglyceride.

lipid values deviated from the population mean values already from the age of 20 to 30 years (Figures 4 and 5), suggesting a time interval of 25 to 35 years with adverse lipid levels before the incident MI. However, this time interval may be shorter, possibly only 10 to 15 years, in individuals with MI at ages 35 to 40 years. Except for the total cholesterol level that was higher than the population mean values from early adulthood almost independent of age at the MI, a delayed age at onset of adverse lipid levels was seen in individuals diagnosed at ages ≥75 years (Figures 4 and 5). In this subgroup, the mean lipid levels were similar to those in individuals without MI until the age of about 50 to 55 years and then became more unfavorable. The unfavorable lipid levels thus seem to be present at least 20 years before an incident MI also in the last decades of life.

Even more remarkable than the variation in age at onset of adverse lipid level was the clear trend toward more severe adverse lipid levels the lower the age at the incident MI (Figures 4 and 5). In the analyses restricted

**Table 2. Estimated Age- and Sex-Specific Differences in Mean Lipid Levels by MI Status (MI vs Non-MI): Longitudinal Analyses of Data From the Tromsø Study 1974 to 2016***

| Lipid variable | Estimated differences (95% CI) in mean lipid levels between individuals with and without a subsequent incident MI | | | | | | |
|---|---|---|---|---|---|---|---|
| | 25y | 35y | 45y | 55y | 65y | 75y | 85y |
| TC, men | 0.92 (0.83 to 1.01) | 0.90 (0.84 to 0.96) | 0.82 (0.77 to 0.87) | 0.71 (0.66 to 0.77) | 0.58 (0.52 to 0.65) | 0.46 (0.37 to 0.55) | 0.34 (0.13 to 0.55) |
| TC, women | 0.41 (0.22 to 0.61) | 0.72 (0.61 to 0.83) | 0.90 (0.81 to 0.99) | 0.94 (0.86 to 1.03) | 0.84 (0.75 to 0.92) | 0.56 (0.46 to 0.66) | 0.11 (−0.10 to 0.32) |
| HDL-C,men | −0.01 (−0.05 to 0.02) | −0.04 (−0.05 to −0.01) | −0.06 (−0.07 to −0.04) | −0.08 (−0.10 to −0.06) | −0.10 (−0.12 to −0.08) | −0.12 (−0.15 to −0.09) | −0.14 (−0.21 to −0.07) |
| HDL-C, women | −0.03 (−0.10 to 0.04) | −0.02 (−0.06 to 0.01) | −0.06 (−0.09 to −0.03) | −0.11 (−0.14 to −0.08) | −0.16 (−0.19 to −0.13) | −0.19 (−0.23 to −0.16) | −0.19 (−0.26 to −0.11) |
| H-C/TC, men | −3.45 (−4.20 to −2.70) | −3.17 (−3.61 to −2.73) | −3.36 (−3.75 to −2.98) | −3.82 (−4.22 to −3.43) | −4.35 (−4.82 to −3.88) | −4.74 (−5.40 to −4.09) | −4.80 (−6.27 to −3.33) |
| H-C/TC,women | −2.66 (−4.06 to −1.26) | −3.65 (−4.39 to −2.90) | −4.58 (−5.21 to −3.94) | −5.30 (−5.88 to −4.71) | −5.67 (−6.28 to −5.06) | −5.54 (−6.26 to −4.81) | −4.75 (−6.21 to −3.29) |
| Triglyceride %, men | 11.2 (7.1 to 15.6) | 11.1 (8.6 to 13.7) | 11.7 (9.3 to 14.2) | 12.3 (9.6 to 15.1) | 12.1 (8.8 to 15.5) | 10.4 (5.7 to 15.2) | 6.5 (−0.04 to 17.9) |
| Triglyceride %, women | 2.6 (−0.07 to 13.0) | 13.9 (8.9 to 19.1) | 18.8 (14.3 to 23.4) | 18.6 (14.3 to 23.0) | 15.4 (10.9 to 20.1) | 11.6 (6.5 to 16.9) | 9.1 (−0.02 to 21.1) |
| Triglyceride-R1, men | 0.32 (0.24 to 0.40) | 0.27 (0.22 to 0.31) | 0.23 (0.18 to 0.27) | 0.20 (0.16 to 0.25) | 0.20 (0.18 to 0.26) | 0.22 (0.13 to 0.31) | 0.26 (0.05 to 0.47) |
| Triglyceride-R1, women | −0.04 (−0.19 to 0.11) | 0.08 (−0.01 to 0.15) | 0.18 (0.12 to 0.25) | 0.25 (0.18 to 0.32) | 0.27 (0.19 to 0.35) | 0.23 (0.13 to 0.33) | 0.11 (−0.10 to 0.32) |
| Triglyceride-R2, men | 2.76 (2.20 to 3.32) | 2.74 (2.43 to 3.06) | 2.63 (2.34 to 2.91) | 2.47 (2.15 to 2.80) | 2.33 (1.91 to 2.74) | 2.26 (1.65 to 2.86) | 2.31 (0.89 to 3.74) |
| Triglyceride-R2, women | −0.19 (−1.27 to 0.88) | 1.02 (0.05 to 1.32) | 2.09 (1.62 to 2.56) | 2.79 (2.31 to 3.28) | 2.89 (2.34 to 3.45) | 2.17 (1.52 to 2.82) | 0.39 (−0.04 to 1.81) |

H-C/TC indicates the ratio between HDL-C and total cholesterol (in %); HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; TC, total cholesterol; TG, nonfasting triglycerides (log-transformed, back-transformed to relative difference); Triglyceride-R1, the ratio between triglyceride and HDL-C and triglyceride-R2, the ratio between triglyceride and HDL-C in proportion of total cholesterol.

*Results are based on linear mixed model with subject as random factor and with age at lipid measurement (1-y intervals), sex (M, W), and MI status at closing date of study (MI, non-MI) as fixed factors (3-way interaction model applied to allow for age- and sex-specific differences in mean lipid level by MI status).

to ages 35 to 49 years, the increase (or decrease) in mean lipid level through the ordered categories of age at the MI was highly significant ($P<0.001$) for all the lipid variables, except the total cholesterol level, which was elevated almost independent of age at the incident MI (Table S2). The less severe adverse lipid levels at ages 35 to 49 years in individuals with MI at ages ≥75 years, and even lack of adverse lipid levels at these ages for some of the lipid variables considered, partly related to a time shift in the age trajectory curve (Figures 4 and 5). Individuals diagnosed with MI <55 years, however, clearly had the most severe adverse lipid levels.

In both sexes, HDL-C in percentage of total cholesterol, and thus also the percentage of non–HDL-C, showed the most consistent association with age at the incident MI (Figure 4C, Table S2). The ratio between triglyceride concentration and HDL-C in proportion of total cholesterol also showed a consistent association with age at the incident MI, especially in women (Figure 5C, Table S2). Notably, the mean triglyceride concentration in women with MI <55 years approximated the one for men with MI <55 years (Figure 5A). Moreover, no clear deviation from population mean triglyceride values was seen in men diagnosed with MI at ages ≥75 years (Figure 5A).

## Sensitivity Analysis

The differences in mean lipid level by MI status were consistently observed, though less pronounced, in the analyses restricted to individuals with at least 5 survey participations to ensure complete longitudinal data and similar age coverage for all individuals (Figure S2). However, the contribution from individuals diagnosed with MI at an age<55 years, and thus with the most severe adverse lipid levels, was limited in these analyses.

# DISCUSSION

The present work is based on longitudinal data on serum lipid levels for a large, population-based cohort in Tromsø, Norway. Adverse lipid levels were defined in terms of deviations from population mean values regardless of clinically recommended levels. Already from ages 20 to 35 years, individuals with a subsequent incident MI had more unfavorable lipid levels than individuals of the same age and sex without MI. Adverse lipid levels were seen 20 to 35 years before the incident MI, possibly sooner before an early-age MI. Our study revealed a clear trend toward more severe adverse lipid levels the lower the age at the incident MI. Thus, adverse lipid levels appear to be important at all ages throughout a lifetime and the potential of early intervention may be substantial. To our knowledge, no previous studies have compared mean lipid levels throughout the adult lifetime in individuals with and

**Table 3. Likelihood Ratio Tests for Heterogeneity by Age and Sex in the Contrast in Mean Lipid Levels by MI Status: Longitudinal Analyses of Data From the Tromsø Study 1974 to 2016***

| | Men | | Women | | Total | |
|---|---|---|---|---|---|---|
| | 2-way interaction (age and MI status) | | 2-way interaction (age and MI status) | | 3-way interaction (age, MI status, and sex) | |
| Lipid variable§ | $\chi^2$† | *P* value‡ | $\chi^2$† | *P* value‡ | $\chi^2$† | *P* value§ |
| TC | 74.99 | <0.001 | 68.15 | <0.001 | 54.09 | <0.001 |
| HDL-C | 33.89 | <0.001 | 47.03 | <0.001 | 9.99 | 0.019 |
| HDL-C/TC | 20.40 | <0.001 | 24.49 | <0.001 | 8.72 | 0.033 |
| Triglyceride (log-transformed) | 1.49 | 0.68 | 11.12 | 0.011 | 6.92 | 0.075 |
| Triglyceride/HDL-C | 4.42 | 0.22 | 31.34 | <0.001 | 23.34 | <0.001 |
| Triglyceride/(HDL-C/TC) | 2.12 | 0.55 | 69.41 | <0.001 | 34.83 | <0.001 |

HDL-C indicates high-density lipoprotein cholesterol; MI, myocardial infarction; TC, total cholesterol.
*Results are based on linear mixed models with subject as random factor and with age at lipid measurement (1-y intervals), sex (men, women), and MI status at closing date of study (MI, non-MI) as fixed factors.
†Value of the test statistic of the likelihood ratio test is based on nested models.
‡*P* value from likelihood ratio test (3 degrees of freedom) for 2-way interaction between age (3 parameters) and MI status in sex-specific analyses.
§*P* value from likelihood ratio test (3 degrees of freedom) for 3-way interaction between age (3 parameters), MI status, and sex in a full factorial model.

without a subsequent incident MI. However, the age curves among individuals without MI in our study were similar to the age patterns observed in other European populations.[9,10,18,20]

The present finding of a clear trend toward more unfavorable lipid levels the earlier the age at diagnosis of MI is analogous to a dose–response relationship indicative of a causal relationship. Although the broad categories of age at diagnosis made it difficult to reveal the exact length of the time period with unfavorable lipid levels before the incident MI, our results are in line with the hypothesis that the adverse effect of a poor lipid profile accumulates over time before an incident MI.[1–3] The less severe adverse lipid level with increasing age at the incident MI may reflect a longer latency time or a higher tolerance for moderately elevated (or reduced) lipid levels. The generally poorer lipid profile in men compared with women, combined with an earlier age at onset of adverse lipid levels, may thus explain the overall higher risk and lower age at onset of incident MI in men.[7,8] It is difficult, though, to take account of such time-related aspects in ordinary age-adjusted analyses of risk of MI. The similar magnitude of the difference in mean lipid levels by MI status in men and women suggests a similar underlying pathogenesis in the development of atherosclerotic-related MI, despite general age-differences. Such a conclusion is also supported by the approximately similar lipid levels observed in men and women with MI at an early age. However, inherent biological sex differences in fat metabolism[26] as well as more favorable lipoprotein characteristics in women[6] may also account for the overall lower risk of MI in women.

In support of the recent conclusions that triglycerides have a causal role in the pathogenesis of atherosclerotic CVD,[27–30] we observed an increase in mean serum triglyceride level with decreasing age at the incident MI. In our study, elevated triglyceride levels appeared to be of particular importance for early-age MI, whereas the potential role of triglyceride in late-age MI was less clear, especially in men. The correlation between triglycerides and cholesterol components, in particular HDL-C,[31] together with inconsistent reports from therapeutic studies,[31,32] have raised the question whether triglyceride level is an independent risk factor for CHD. In addition, it may be difficult to distinguish between direct and indirect effects when it comes to underlying biological processes. Abnormality in the clearance process of triglyceride levels has been proposed to lead to a proatherogenic milieu,[33–35] whereas HDL-C has been suggested to play an important role for the triglyceride clearance process,[36,37] possibly with age as a modifying factor.[38] Consistent with a previous report of a more rapid clearance of triglyceride levels in women than men,[26] and in support of the theory that HDL-C may play a role in this process, we found high levels of triglyceride despite proportionally high HDL-C levels more often in men than women. However, the subgroup with this adverse characteristic was small. Triglyceride levels have traditionally been measured in fasting blood, but the importance of focusing on nonfasting triglyceride levels has been accentuated in a recent review.[29] Nonfasting levels were used in the present study.

Consistent with previous findings that the ratio between HDL-C and total cholesterol is a better predictor for CHD death than each variable alone,[39] we found a more pronounced association between age at the incident MI and HDL-C in percentage of the total cholesterol level than with each separate cholesterol variable. The ratio between HDL-C and total cholesterol level also reflects the proportion of non–HDL-C, mainly LDL-C. However, the nonfasting lipid levels precluded a

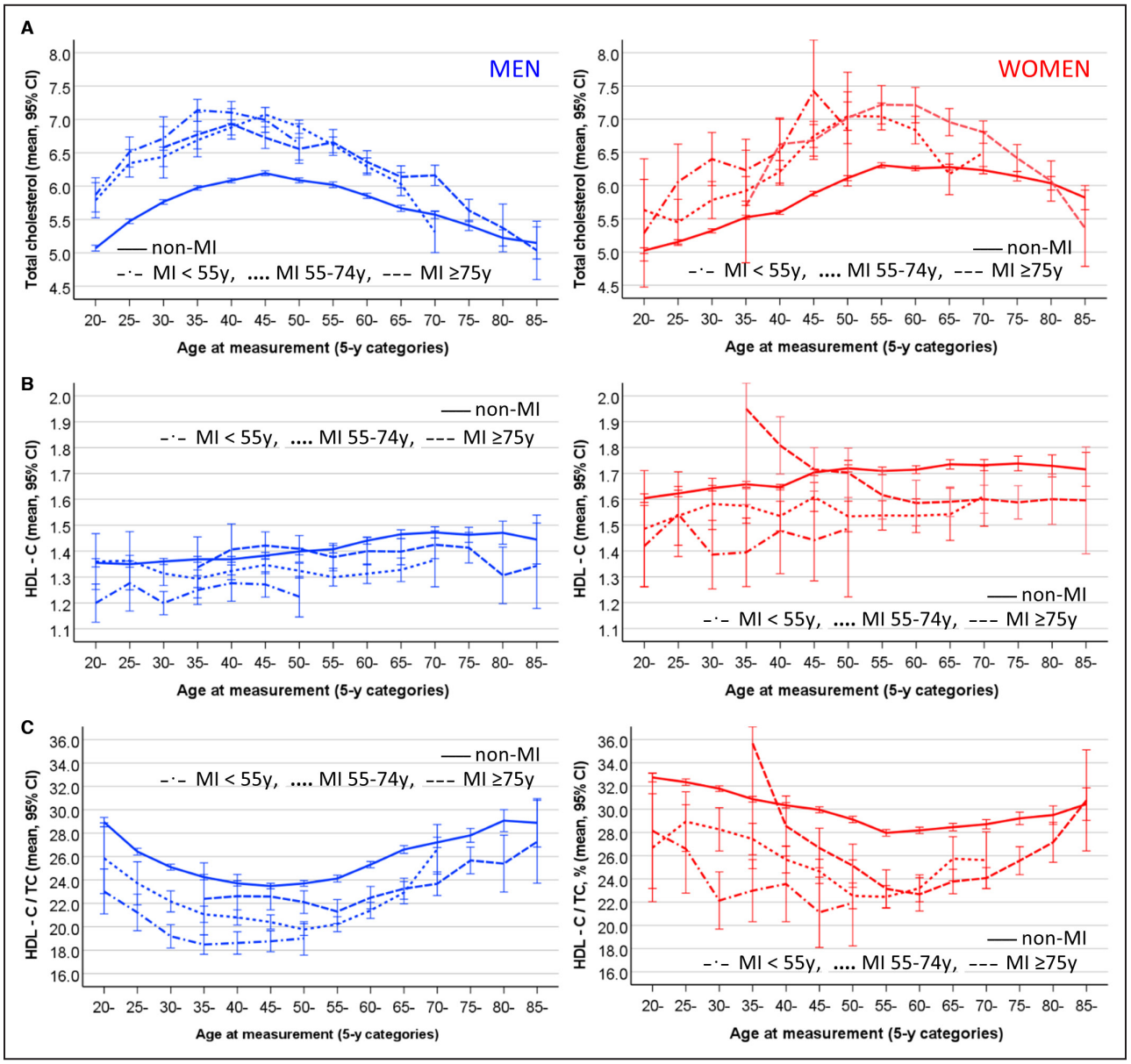


**Figure 4. Mean lipid levels by age, sex, and age at MI: The Tromsø Study 1974 to 2016.**
Sample mean values with 95% CI of (**A**) TC (mmol/L), (**B**) HDL-C (mmol/L), and (**C**) HDL-C in percentage of TC (HDL-C/TC, %) during the adult lifetime in men (left column) and women (right column) with and without a subsequent incident MI (MI and non-MI, respectively), with the MI group further categorized by age at the diagnosis of MI.HDL–C indicates high-density lipoprotein cholesterol; MI, myocardial infarction; and TC, total cholesterol.

more accurate calculation of LDL-C. The ratio between triglyceride levels and HDL-C in the proportion of total cholesterol also showed a consistent association with age at the incident MI, especially in women. This association appeared to be even more pronounced than the one with the simple ratio between triglyceride level and HDL-C. This ratio has previously been identified as an early marker for insulin resistance and susceptibility to development of atherosclerosis[40,41] and as a predictor of CVD.[40,42–44] A favorable level, calculated on the basis of recommended levels for each single variable, would be <1.7 for men and <1.3 for women. In our study population, only men diagnosed with MI had a mean value of this ratio >1.7. To our knowledge, no previous study has paid attention to the ratio between triglyceride concentration and HDL-C in the proportion of total cholesterol. A favorable value of this ratio would be ≤6.8 in both sexes, using 0.25 as the recommended level for HDL-C in the proportion of total cholesterol. Only women without MI had mean levels below this value in our cohort, a finding that is interesting since women in general constitute a low-risk group. Further analyses are needed to

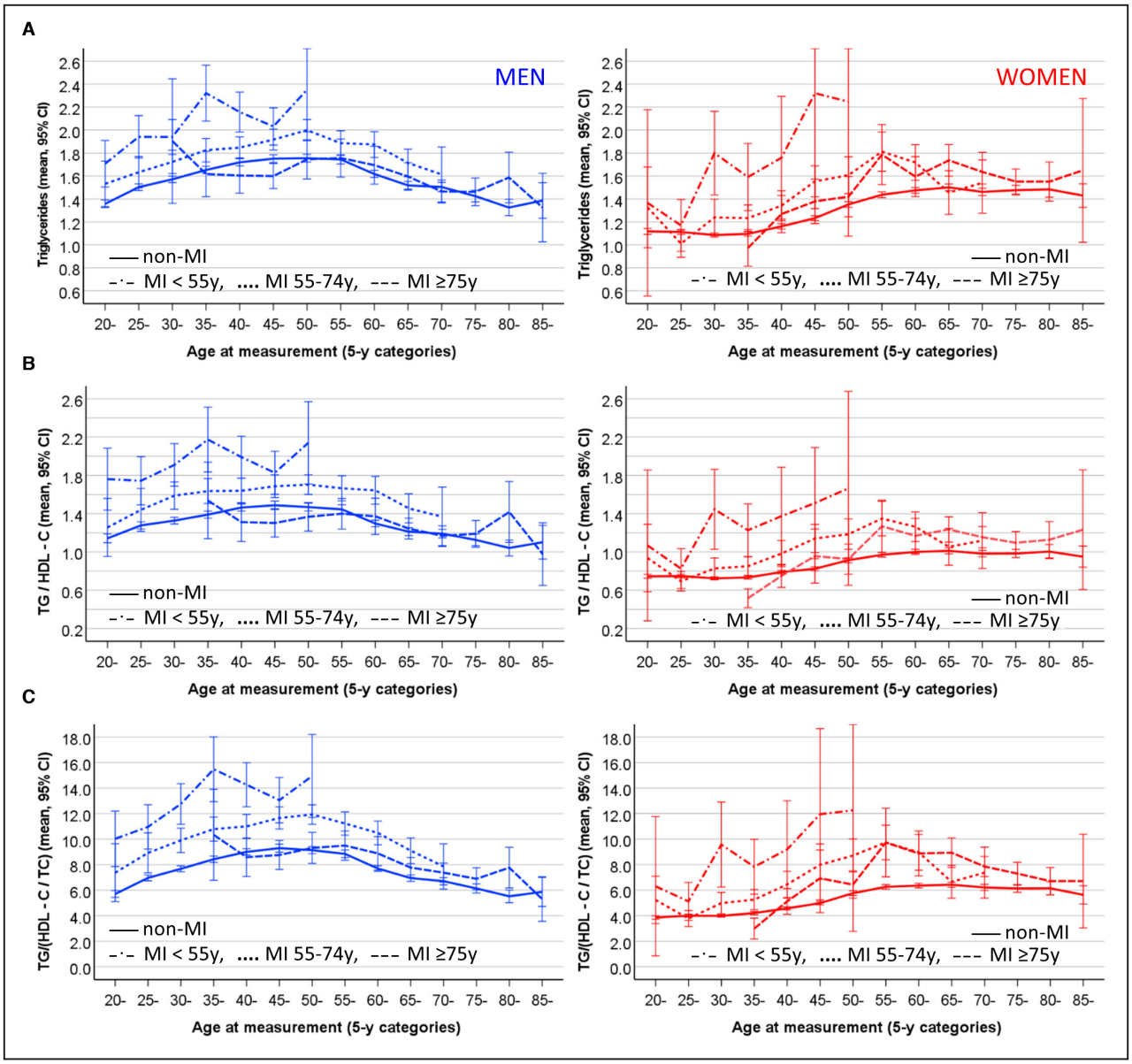


**Figure 5. Mean lipid levels by age, sex and age at MI: The Tromsø Study 1974 to 2016.**
Sample mean values with 95% CI of (**A**) TG (mmol/L), (**B**) the ratio between TG and HDL-C (TG/HDL-C), and (**C**) the ratio between TG and HDL-C in proportion of TC (TG/[HDL/TC]) during the adult lifetime in men (left column) and women (right column) with and without a subsequent incident MI (MI and non-MI, respectively), with the MI group further categorized by age at the diagnosis of MI. HDL–C indicates high-density lipoprotein cholesterol; MI, myocardial infarction; TC, total cholesterol; and TG, triglyceride.

evaluate whether this triglyceride ratio can be used as a predictor of the risk of MI. Nevertheless, the present findings may indicate that the internal balance between the levels of the different lipid variables is of importance for long-term adverse effects.

## Strength and Limitations

A major strength of the present study is the access to repeated measurements on serum lipid levels for a large number of participants in population-based health surveys, with retrospective linkage to information on diagnosis of MI. At the time of the lipid measurement, none of our study participants had suffered an MI, and in theory there is no distinction between the groups that are compared except the knowledge of a future diagnosis. A limitation, though, is the lack of complete longitudinal observations due to variation in age at participation and the number of surveys attended. The total age span covered was 70 years (20–89 years), but the longest individual age coverage in our study population was 42 years for men and 37 years for women. Undiagnosed MI or diagnoses after closing date of study may lead to misclassification bias. However, the proportion of

potentially misclassified non-MI cases will be low compared with the truly classified non-MI cases, also in view of the prevalence of MI. A potential misclassification bias will, if anything, lead to an underestimation of the difference in mean lipid levels by MI status.

Cohort and period effects may influence the observed age patterns but in a similar way in the groups compared. Such time-related effects are thus not expected to lead to severe bias in the estimated differences in mean lipid values by MI status. The serum lipid-level measurements were obtained from health surveys carried out in the period 1974 to 2016, and the use of lipid-lowering drugs increased during this period, especially after 1994 among individuals aged ≥50 years.[45] Thus, the apparent improvement in lipid profile with increasing age and the less pronounced differences in mean lipid levels by MI status among elderly people may partly reflect a treatment effect but also a healthy survivor effect.

Dietary and lifestyle factors, clinical characteristics, chronic diseases, and genetic factors influence lipid levels. Nevertheless, to uncover at what age and how long before the incident MI an adverse lipid profile manifests, we compared age- and sex-specific mean lipid values between individuals with and without a subsequent incident MI, regardless of underlying causes of either favorable or unfavorable lipid levels. The longitudinal design of our study made it possible to evaluate consequences of long-term exposure to adverse lipid levels and to distinguish these effects from normal age-related changes. In a preventive perspective, however, identification of modifiable factors of importance for lipid levels, as well as effective intervention strategies, is essential to reduce the burden of CHD, at both the individual and community level.

## CONCLUSIONS

The present exploratory analyses indicate that there is, on average, a period of 20 to 35 years with adverse lipid levels before an incident MI, with a clear trend toward more severe adverse levels the earlier the age at the diagnosis. Intervention strategies targeting improved lipid profiles at ages when awareness of MI is still low may thus have a substantial impact on the subsequent risk of MI. Results from our study highlight the need to monitor lipid levels at all ages during a lifetime. The deviation from population mean values in individuals with a subsequent incident MI appears to be equally large for women and men, indicating a similar cause of MI despite marked age differences. The study results can be used to define time-dependent exposure factors and critical points in time relevant for intervention. These factors may also increase our knowledge about sex differences in the risk of MI.

## ARTICLE INFORMATION

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### Disclosures

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### Supplemental Material

Data S1
Tables S1–S2
Figures S1–S2

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## SUPPLEMENTAL MATERIAL

# Lipid levels during adult lifetime in men and women with and without a subsequent incident myocardial infarction. A longitudinal analysis of data from the Tromsø Study 1974-2016.

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## Supplemental Methods

### Specification of the three-way interaction model

The fixed effect part of the full factorial three-way interaction model was defined as follow

$$Y_{age} = \alpha_{ij} + (\beta_1 * X_{age} + \beta_2 * X_{age}^2 + \beta_3 * X_{age}^3) + \beta_4 * X_{sex} + \beta_5 * X_{MI} + \beta_6 * X_{sex} * X_{MI}$$
$$+ (\beta_7 * X_{sex} * X_{age} + \beta_8 * X_{sex} * X_{age}^2 + \beta_9 * X_{sex} * X_{age}^3)$$
$$+ (\beta_{10} * X_{MI} * X_{age} + \beta_{11} * X_{MI} * X_{age}^2 + \beta_{12} * X_{MI} * X_{age}^3)$$
$$+ (\beta_{13} * X_{sex} * X_{MI} * X_{age} + \beta_{14} * X_{sex} * X_{MI} * X_{age}^2 + \beta_{15} * X_{sex} * X_{MI} * X_{age}^3)$$

where $Y_{age}$ reflects the lipid measurement at a particular age, with $X_{age}$, $X_{age}^2$ and $X_{age}^3$ representing the linear, quadratic and cubic terms in the cubic polynomial used for modeling the non-linear age-trajectories during ages 20-89 years (1-year intervals, continuous variables). $X_{sex}$ and $X_{MI}$ and are indicator variables for sex (i=0,1) and MI-status at closing date of study (j=0,1), respectively (categorical variables). The estimated regression model, with numerical values for all the regression coefficients ($\beta_k$, k=1-15) was used to calculate the model-based predicted mean lipid values during adult lifetime in the four subgroups defined by sex and MI-status. The predicted mean lipid values are graphically displayed in Figure 2-3. The corresponding age- and sex-specific differences in mean lipid values by MI-status (with 95% confidence intervals) are shown in Table 2.

***- statistical test of three-way interaction between sex, age and MI-status***

The likelihood ratio (LR) tests of the three-way interaction between sex, age and MI-status in the full factorial model provide a formal statistical test of sex-differences in the contrast in age-trajectories by MI-status. The value of the test statistic was defined by the difference in the -2log-likehood value from analyses with and without the three-way interaction terms ($\beta_{13}$, $\beta_{14}$ and $\beta_{15}$) included in the model (nested models). The LR-test statistic is asymptotically chi-squared distributed with 3 degrees of freedom (DF). The DF reflects the difference in the number of parameters in the two nested models. The p-values for the tests of three-way interaction for each lipid variable are presented in Table 3.

### Specification of the two-way interaction model (sex-specific analyses)

Sex-specific analyses were needed to perform meaningful statistical testing of the two-way interaction between MI-status and age. The two-way interaction model applied in the analyses among men and women, respectively, was defined as follow

$$Y_{age} = \alpha_i + (\beta_1 * X_{age} + \beta_2 * X_{age}^2 + \beta_3 * X_{age}^3) + \beta_4 * X_{MI}$$
$$+ (\beta_5 * X_{MI} * X_{age} + \beta_6 * X_{MI} * X_{age}^2 + \beta_7 * X_{MI} * X_{age}^3)$$

***- statistical test of two-way interaction between age and MI-status***

The likelihood ratio (LR) tests of the two-way interaction between age and MI-status provide a formal statistical test of heterogeneity in age-trajectories by MI-status. The value of the test statistic was defined by the difference in the -2log-likehood value from analyses with and without the two-way interaction terms ($\beta_5$, $\beta_6$ and $\beta_7$) included (nested models). The test statistic is asymptotically chi-squared distributed with 3 degrees of freedom (DF). The P-values from the tests of two-way interaction for each lipid variable among men and women, respectively, are presented in Table 3.

**Table S1. Pearson (Spearman) correlation coefficient* between triglyceride concentration and cholesterol levels in men and women by MI-status (MI, non-MI; status at closing date of study). The Tromsø Study 1974-2016.**

| | MEN | | WOMEN | |
|---|---|---|---|---|
| | Non-MI | MI | Non-MI | MI |
| **Triglyceride and** | | | | |
| - total cholesterol | +0.27 (+0.29) | +0.24 (+0.28) | +0.32 (+0.36) | +0.35 (+0.33) |
| - HDL-C | -0.35 (-0.46) | -0.28 (-0.44) | -0.37 (-0.39) | -0.41 (-0.44) |
| - HDL-C/total chol. † | -0.47 (-0.58) | -0.41 (-0.55) | -0.52 (-0.57) | -0.55 (-0.58) |

MI indicates incident myocardial infarction; HDL-C, high-density lipoprotein cholesterol.

* Based on data from all single time-points (all ages).

† Ratio between total cholesterol and HDL-C.

**Table S2. Estimated overall difference in mean lipid level at ages 35-49 years by age at MI. Longitudinal analyses of data from the Tromsø Study 1974-2016.[*]**

| Lipid variable | Difference in mean lipid level (95% CI), MI (by age at MI) vs. non-MI | |
|---|---|---|
| | **MEN** | **WOMEN** |
| **Total cholesterol (TC)** | | |
| - non-MI | 0.00 (reference) | 0.00 (reference) |
| - MI < 55 yr | 1.01 (0.89,1.13) | 1.02 (0.71,1.32) |
| - MI 55- 74 yr | 0.88 (0.80,0.95) | 0.72 (0.61,0.84) |
| - MI ≥ 75 yr | 0.77 (0.62,0.91) | 0.79 (0.59,1.00) |
| p-value, linear trend[†] | 0.19 | 0.067 |
| **HDL-cholesterol (HDL-C)** | | |
| - non-MI | 0.00 ( reference) | 0.00 (reference) |
| - MI < 55 yr | -0.10 (-0.14,-0.07) | -0.21 (-0.32,-0.10) |
| - MI 55- 74 yr | -0.04 (-0.07,-0.02) | -0.08 (-0.13,-0.04) |
| - MI ≥ 75 yr | 0.04 ( 0.02, 0.10) | 0.09 ( 0.01, 0.16) |
| p-value, linear trend[†] | <0.001 | <0.001 |
| **HDL-C / TC (%)** | | |
| - non-MI | 0.00 ( reference) | 0.00 ( reference) |
| - MI < 55 yr | -5.29 (-6.02,-4.56) | -7.48 (-9.81,-5.15) |
| - MI 55- 74 yr | -3.01 (-3.52,-2.51) | -4.65 (-5.54,-3.76) |
| - MI ≥ 75 yr | -1.07 (-2.22, 0.08) | -1.94 (-3.54,-0.35) |
| p-value, linear trend[†] | <0.001 | <0.001 |
| **Triglycerides, TG (%)** | | |
| - non-MI | 1.00 ( reference) | 1.00 ( reference) |
| - MI < 55yr | 28.2 ( 21.9, 0.7) | 49.6 (31.7, 69.9) |
| - MI 55- 74 yr | 9.7 ( 6.3, 13.2) | 17.0 (11.4, 22.9) |
| - MI ≥ 75 yr | -0.05 (-0.11, 34.7) | 7.3 (-0.03, 17.3) |
| p-value, linear trend[†] | <0.001 | <0.001 |
| **TG / HDL-C** | | |
| - non-MI | 0.00 ( reference) | 0.00 ( reference) |
| - MI < 55 yr | 0.57 ( 0.44, 0.70) | 0.58 ( 0.40, 0.76) |
| - MI 55- 74 yr | 0.20 ( 0.11, 0.28) | 0.22 ( 0.15, 0.29) |
| - MI ≥ 75 yr | -0.18 (-0.38, 0.02) | 0.01 (-0.12, 0.13) |
| p-value, linear trend[†] | <0.001 | <0.001 |
| **TG / (HDL-C / TC)** | | |
| - non-MI | 0.00 ( reference) | 0.00 ( reference) |
| - MI < 55 yr | 5.53 ( 4.63, 6.44) | 4.91 (3.65, 6.17) |
| - MI 55- 74 yr | 2.24 ( 1.62, 2.86) | 2.15 (1.67, 2.64) |
| - MI ≥ 75 yr | -0.51 (-1.93, 0.92) | 0.88 (0.00, 1.76) |
| p-value, linear trend[†] | <0.001 | <0.001 |

MI indicates myocardial infarction.

[*] Results based on linear mixed model with subject as random factor, and with age and MI-status (MI, non-MI) combined with age at MI-categories, as fixed factors (no-interaction model). Sex-specific analyses in the age interval 35-49 years (age modelled as linear trend).
[†] Likelihood ratio test for linear trend in mean lipid levels through the ordered categories of age at the diagnosis of MI (the non-MI group excluded from the analyses).

**Figure S1. Scatterplot between triglyceride levels and high-density lipoprotein cholesterol (HDL-C) in % of total cholesterol level. The Tromsø Study 1974-2016.**

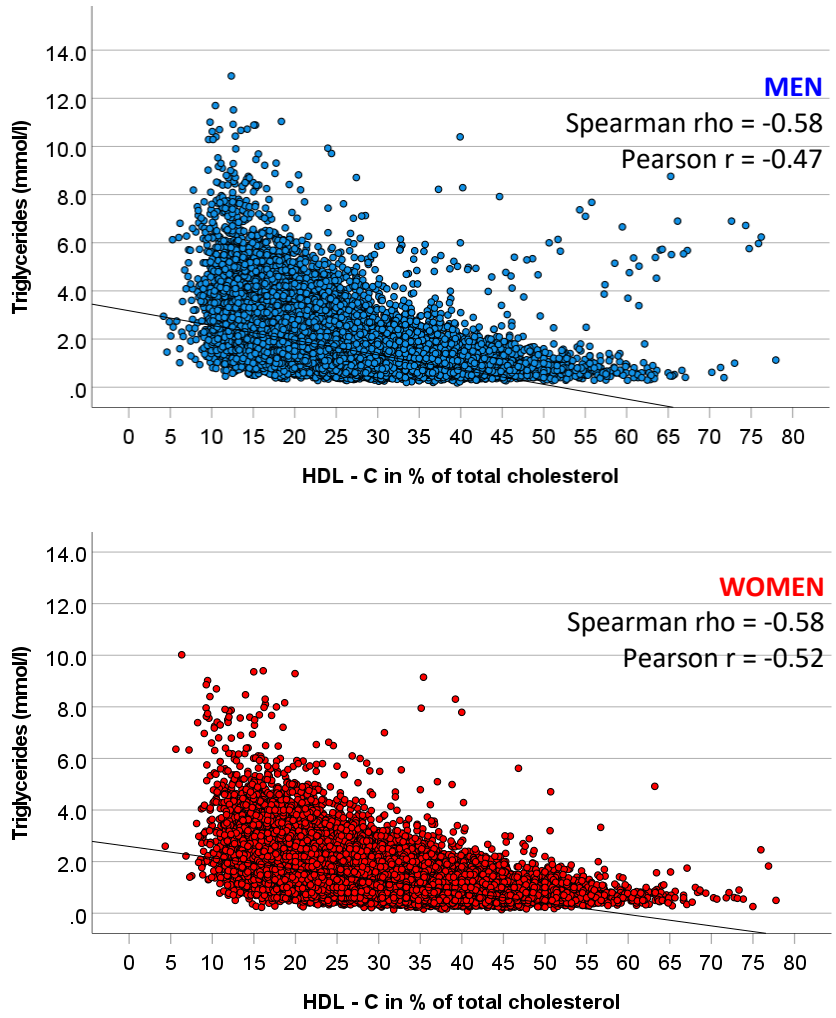
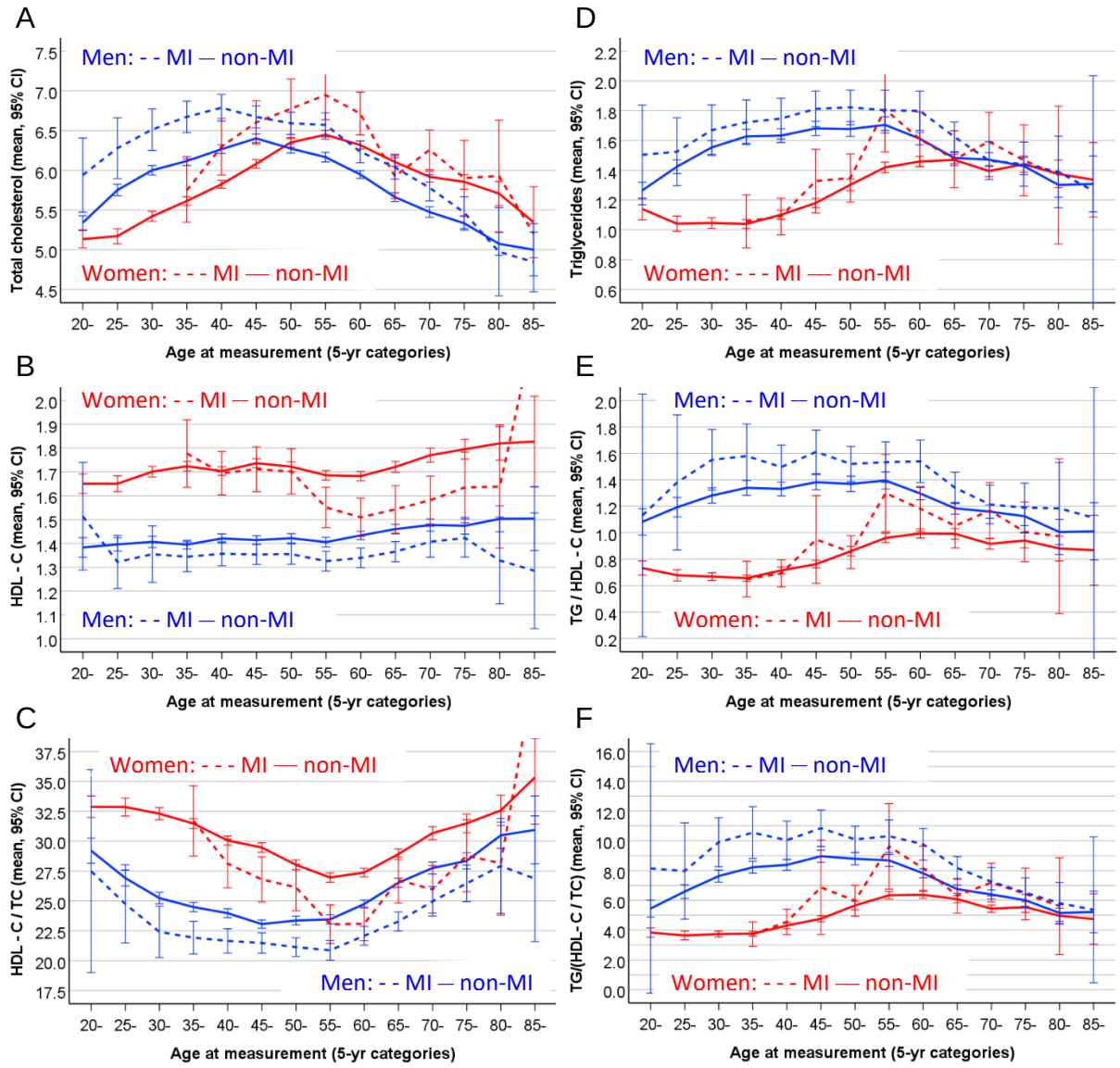


**Figure S2. Sensitivity analyses. Mean lipid level by age, sex and MI-status (MI, non-MI) among individuals with 5-7 survey participations. The Tromsø Study 1974-2016.**




Sample mean values with 95% CI of **(A)** total cholesterol (mmol/L), **(B)** high-density lipoprotein cholesterol (HDL-C, mmol/L), **(C)** HDL-C in % of total cholesterol (HDL-C/TC, %), **(D)** triglycerides (mmol/L), **(E)** the ratio between triglycerides and HDL-C (TG/HDL-C) and **(F)** the ratio between triglycerides and HDL-C in proportion of total cholesterol (TG/(HDL-C/TC)) during adult lifetime in men and women with and without a subsequent incident myocardial infarction (MI and non-MI, respectively).