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Lipid re-screening: what is the best measure and interval?

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ABSTRACT

Objectives To estimate the long-term true change variation (‘signal’) and short-term within-person variation (‘noise’) of the different lipid measures and evaluate the best measure and the optimal interval for lipid re-screening.

Design Retrospective cohort study from 2005 to 2008.

Setting A medical health check-up programme at a centre for preventive medicine in a teaching hospital in Tokyo, Japan.

Participants 15 810 apparently healthy Japanese adults not taking cholesterol-lowering drugs at baseline, with a mean body mass index of 22.5 kg/m² (SD 3.2).

Main outcome measures Annual measurement of the serum total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and calculation of the ratio of TC/HDL and LDL/HDL. Measurement of the ratio of long-term true change variation (‘signal’) to the short-term within-person variation (‘noise’) for each measure.

Results At baseline, participants (53% male) with a mean age of 49 years (range 21–92) and a mean TC level of 5.3 mmol/l (SD 0.9 mmol/l) had annual check-ups over 4 years. Short-term within-person variations of TC, LDL, HDL, TC/HDL, and LDL/HDL were 0.12 (coefficient of variation (CV) 8.4%), 0.08 (CV 9.4%), 0.02 (CV 8.0%) mmol/l², 0.08 (CV 7.9%) and 0.05 (CV 10.6%), respectively. The ratio of signal-to-noise at 3 years was largest for TC/HDL (1.6), followed by LDL/HDL (1.5), LDL (0.99), TC (0.8) and HDL (0.7), suggesting that cholesterol ratios are more sensitive re-screening measures.

Conclusion The signal-to-noise ratios of standard single lipid measures (TC, LDL and HDL) are weak over 3 years and decisions based on these measures are potentially misleading. The ratios, TC/HDL and LDL/HDL, seem to be better measures for monitoring assessments. The lipid re-screening interval should be >3 years for those not taking cholesterol-lowering drugs.

INTRODUCTION

Dyslipidaemia is common in industrialised countries,1 including Japan,2 and is an important modifiable risk factor for coronary heart disease (CHD) and cardiovascular disease (CVD).3–5 Large randomised controlled studies and meta-analysis studies have established that cholesterol-lowering treatment reduces CHD morbidity and mortality.3 6–8 Thus, cholesterol level screening is important for adults to identify those at risk of CVD and is widely available.9 10

Screening the cholesterol level includes interpretation of the initial level and also that of a series of sequential levels over time,11 in which we should consider the variations of both short-term within-person and long-term among individuals in the population.12 Lipid guidelines for primary prevention of CVD and CHD recommend a targeting level for lipid level and how to interpret initial measurements; however, they rarely specify subsequent monitoring in primary prevention, and guidelines vary in their recommendation. In the United Kingdom, the National Institute for Clinical Excellence13 14 for the primary prevention of CVD recommends that people aged 40–74 years without a history of CVD should have total cholesterol (TC) and high-density lipoprotein cholesterol (HDL) measured; however, the optimal interval for these measurements is not provided.

On the other hand, in the United States, the National Cholesterol Education Program in Adults1 recommends that all adults aged >20 years have a fasting lipoprotein profile that includes TC, low-density lipoprotein cholesterol (LDL), HDL and triglycerides once every 5 years. Moreover, the United States Preventive Services Task Force15 recommends that doctors routinely screen men aged ≥35 years and women aged ≥45 years for lipid disorders. Again, however, the optimal re-screening interval is unclear. Even when guidelines suggest screening intervals, the basis for these suggestions is not provided and no guidelines consider within-person and long-term variation in their re-screening strategies.

Detecting dyslipidaemia and intervening early can reduce the impact but it also has some important drawbacks such as inconvenience and cost; in addition, false-positive results may be obtained that can lead to inappropriate action.11 16 A good monitoring test should correlate with the final clinical outcomes but also differentiate changes in the condition (signal) from the background of measurement variability (noise).12 Considering such variations could avoid leading to inappropriate intervention or minimise the harm.12 17–19 Thus, in choosing test options, the signal-to-noise (S/N) ratio may be a key factor in determining the value of the test for monitoring.16

We, therefore, aimed to estimate the variation in long-term true changes in the different lipid profile measures and the short-term within-person variations and thus estimate the S/N ratio in cholesterol screening. Since several previous studies have suggested that lipid ratios (TC/HDL and LDL/HDL) have greater independent predictive values for CHD than serum TC or LDL levels,20–22 we compared S/N ratio among different types of cholesterol measures, including...
We calculated the variance of differences between the true increase of a patient not collected as part of the dataset. To preserve patient confidentiality, direct patient identifiers were not collected as part of the dataset.

METHODS
Study participants
Between January and December 2005, we consecutively enrolled all people attending our Centre for Preventive Medicine at St Luke’s International Hospital in Tokyo, Japan for the health check-up programme. The purpose of this programme is to promote public health through early detection of chronic diseases and disease risk factors. In Japan, the industrial Safety and Health Law obliges all workers and their family to undergo an annual health check-up in their workplaces. About 30 companies and local government organisations in Tokyo, Japan have made a contract with our centre to provide this check-up for their employees. Thus, at our centre, around 80% of participants are employees and their dependants of various companies and local government organisations in Tokyo, Japan. The cost of the medical examination is largely paid for by the employers. Since many participants are expected to have repeated examinations, we took advantage of this opportunity to conduct a follow-up study. The remaining 20% of participants are citizens of Tokyo who individually registered for the programme and paid for it without company sponsorship.

Data collection
We collected data from adults (>20 years) who had undergone an annual health check-up from 2005 to 2008 at the Centre for Preventive Medicine in St Luke’s International Hospital in Tokyo, Japan. We excluded people who took cholesterol-lowering drugs at baseline (figure 1). Two investigators independently extracted and recorded information using a structured data form. A consensus was reached after discussion for any points of disagreement. St Luke’s International Hospital ethical committee institutional review board approved all aspects of this study. To preserve patient confidentiality, direct patient identifiers were not collected as part of the dataset.

Measurements
An annual check-up consists of demographic information, medical history, initial evaluation (vital signs and laboratory data) and treatments provided. Laboratory data includes lipids (TC, LDL cholesterol, HDL cholesterol and triglyceride), fasting plasma glucose, HbA1c and thyroid-related hormones. Venous blood was drawn for measurements after an overnight fast and analysed at a central laboratory. Direct LDL and direct HDL measurements were performed in the Central Laboratory at the Centre for Preventive Medicine in St Luke’s International Hospital by the LDL-cholesterol kit and HDL-cholesterol kit, respectively, provided by Sekisui Medical (Tokyo, Japan).

Long-term true change and short-term within-person variations
We used the direct method to estimate variations in long-term true change among patients and short-term within-person variation.25 We calculated the variance of differences between the baseline value in 2005 and each subsequent year. Based on the ‘variogram’ method, we used a linear extrapolation backward from the longer-term measurements and evaluated what the apparent variance would be at baseline.17 By subtracting this variance at baseline (equal to twice short-term within-person variation) from this variance of change, we estimated the true long-term change among patients.

Censored values
Some patients in our study started taking cholesterol-lowering drugs after baseline. To avoid including changes caused by cholesterol-lowering treatment while minimising selection bias, we ‘censored’ such data and replaced subsequent values with the previous one for each following measurement (‘last observation carried forward’). For the sensitivity analysis, we also excluded all observations from patients who started taking a cholesterol-lowering drug.

Detecting the ratio of signal (long-term changes) to noise (within-person variations)
We used the S/N ratio to estimate the optimal interval and the best measure for re-screening.17 A true increase of a patient’s cholesterol level consists of the average change of the whole group over time (signal) and the short-term within-person variation around the average change (noise). When monitoring, we aim to detect the people who drift from the average population. This would be reflected as an increase in long-term variation of the overall population. Therefore, the long-term variation will also be part of the signal. In a good monitoring test, the signal needs to be large relative to noise; thus we calculated the S/N ratio by dividing signal by noise and estimated the optimal rescreening interval when the ratio was >1.

Statistical methods
All analyses were conducted by SPSS statistical software V 15.0J (SPSS Japan, Tokyo, Japan). Responses were analysed using descriptive statistics, including mean, variance, SD and percentages. A coefficient of variance was calculated by the SD divided by the mean cholesterol level at baseline. The 95% CIs were calculated using normal approximation methods.

RESULTS
Demographic data
From January 2005 to July 2008, 15 810 people underwent annual check-ups (figure 1). The mean age of patients was 49.3 years old (SD 12.2, range 21–92) and 55% of patients were male. Other primary characteristics of patients are shown in table 1. The average TC, LDL cholesterol and HDL cholesterol level at baseline were 5.3 mmol/l (SD 0.9), 3.0 mmol/l (SD 0.8) and 1.6 mmol/l (SD 0.4), respectively. The mean ratio TC/HDL and LDL/HDL level at baseline were 3.5 (SD 1.0) and 2.0 (SD 0.8), respectively. Figure 2 shows the trends of each mean lipid level from 2005 to 2008.
**Short-term, within-person variation**

Figure 3 shows the direct estimates of the variance of change in each of five lipoprotein profiles over 4 years. Based on this figure, a linear backward extrapolation of the variogram method estimated that the variances of difference among individual cholesterol levels at baseline were 0.24, 0.16, 0.03 mmol²/l², 0.16 and 0.10 for TC, LDL, HDL, TC/HDL and LDL/HDL, respectively. The SDs of the short-term variations (square root of half the variance of the difference) were 0.35, 0.28, 0.13 mmol/l, 0.28 and 0.22 for TC, LDL, HDL, TC/HDL and LDL/HDL, respectively. In addition, the coefficients of variation were 6.4%, 9.4%, 8.0%, 7.9% and 10.6% for TC, LDL, HDL, TC/HDL and LDL/HDL, respectively.

**Long-term, true change variation**

Figure 3 indicates the increase in variance of differences for all lipoprotein profiles over time. We divided the variances of difference into two components—short-term within-person variation at baseline and long-term variation. The long-term variation increased over time from 0 at baseline to 0.10 (SD 0.32), 0.08 (SD 0.29), 0.012 (SD 0.11) mmol²/l², 0.12 (SD 0.05) and 0.07 (SD 0.27) by year 5 for TC, LDL, HDL, TC/HDL and LDL/HDL, respectively.

**DISCUSSION**

**Summary of findings**

This large population survey of adults not taking cholesterol-lowering drugs suggested that the lipid ratios of TC/HDL and LDL/HDL are the best monitoring predictors for re-screening to identify those at risk for CVD. The optimal interval for re-screening should be in the region of 3 years or more.

**Comparison with other reports and implications**

The estimated within-person coefficient of variation (CV) of 6.4% for TC levels is comparable to values found in the previous studies.24 25 In the MRC Mild Hypertension Trial (n=14,600),
Thompson and Pocock\textsuperscript{24} showed that for measurements 1 year apart, the within-person CV was 7%. In a meta-analysis of 30 studies, Smith et al\textsuperscript{25} reported that the within-person CV for TC averaged 6.1% (95% CI 5.6% to 6.6%). However, previous studies reported that within-person variations increased with the sampling interval\textsuperscript{25--28} and were influenced by the analytical methods.\textsuperscript{25} For example, a study of 41 healthy volunteers\textsuperscript{26} showed that for a median of 24 h, CV was 2--5%, whereas for 4 days or longer, it increased to 4--5%.

Our study showed that the estimated within-person CV for LDL (9.4%) was slightly higher than TC (6.4%) and HDL (8.0%). The results are comparable with the previously mentioned meta-analysis.\textsuperscript{25} Smith et al\textsuperscript{25} estimated that biological CVs were 9.5% (95% CI 8.1% to 10.7%), 6.1% (95% CI 5.6% to 6.6%) and 7.4% (95% CI 6.7% to 8.1%) for LDL, TC and HDL, respectively. Although we directly measured LDL, in contrast to the previous study\textsuperscript{25} in which LDL was calculated by Friedewald equation, the direct LDL assay could not reduce the variability in LDL compared with the conventional LDL calculation.\textsuperscript{29}

Our survey indicates that most of the variation in the first few years is due to short-term within-person variation as the long-term change of variation per year slightly increased. For example, the long-term change of variation for TC from baseline to 3 years is smaller than short-term within-person variation based on a 0.8 S/N ratio for TC at 3 years in our study. Thus, if a patient is in a relatively stable condition, as was our screening population, measuring too frequently, such as every year, is potentially misleading and random fluctuations that occur in clinical measurements may mislead us into changing treatment unnecessarily.\textsuperscript{12,17}

Based on the S/N ratio in our study, we suggest that the interval of re-screening for dyslipidaemia could be at least 3 years for adults not taking cholesterol-lowering drugs. These intervals are almost compatible with those in most current guidelines,\textsuperscript{3,15} which are based on expert opinion. However, to determine the optimal interval of the individual level, we should consider the change of patients' lifestyle and treatment during their monitoring. On the other hand, risk factors of CVD, such as blood pressure and diabetes, should be taken into consideration for the overall risk assessments; however, in this study, we have focused on the variation of lipid profile in this increase over time and its impact on the assessment of lipid re-screening to evaluate the interval.

Our survey showed that the two lipid ratios are better monitoring predictors than single standard lipids including TC, LDL and HDL since their S/N ratios (1.6 for TC/HDL and 1.5 for LDL/HDL) at 3 years are higher than those of other lipids measures (0.8 for TC and 0.99 for LDL). As for initial risk measurement, several previous cohort studies,\textsuperscript{20--22,30} a meta-analysis study,\textsuperscript{31} and the Joint British Societies’ (JBS 2) guidelines\textsuperscript{32} suggest that lipid ratios (TC/HDL and LDL/HDL) also have greater independent predictive values for CHD than individual serum TC or LDL level, whereas current guidelines\textsuperscript{3,15} for primary prevention of CHD do not emphasise the use of these lipid ratios for screening. In choosing a good monitoring tool, in addition to the clinical validity of the initial risk measurements, the S/N ratio needs to be high (at least >1.0) to address potential false-positive results due to short-term within-person variation.\textsuperscript{12,17} Therefore, the ratio of TC/HDL or LDL/HDL might be used not only as an initial risk assessment, but also as a monitoring measurement over time.

In this study, we did not examine the other initial risk measurements of lipids, such as apoA, apoB and apoA/apoA ratio, since we were interested in the screening of lipids measured routinely in many clinical practice setting. However, similar research would be worthwhile for the apolipoproteins and other biomarkers of CVD risk to evaluate their optimal interval. Some guidelines recommend that LDL is calculated non-directly rather than measured directly. Thus, we carried out our analysis with the direct LDL measurements and also estimated non-direct LDL using the Friedewald formula. We concluded that the values are comparable and, therefore, reported only the results of direct LDL in our study.

**Limitations**

Our survey has several limitations. First, we collected data from only one institution in Tokyo, Japan. Although the sample size is large, findings might not be generalised to other populations. Second, there may be some change in variation because of the need to impute future values in patients who began taking cholesterol-lowering drugs. However, this is unlikely to make a large.
difference to our conclusions because of its small proportion (4.8%). Third, a substantial proportion of patients were not followed up for all 4 years. If the rate of change of cholesterol was different for those patients, our results might be biased. Finally, although we used the direct method to estimate within-person variation, we did not use other models for analysis, such as a linear mixed model. However, we think that the direct method results in higher estimates of long-term variation because it is more conservative in indicating the likelihood of early change, and therefore more likely to report shorter monitoring intervals.

CONCLUSION
The SN ratios of a single lipid measure (TC, LDL and HDL) are weak over 3 years and decisions based on these measures are potentially misleading. The ratios of TC/HDL and LDL/HDL are better measures for both initial assessment of CVD risk and for continuing monitoring. The interval should be more than 3 years for monitoring assessment.

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Competing interests None.

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