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CURRENT OPINION

Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points—a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine

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Aims To critically evaluate the clinical implications of the use of non-fasting rather than fasting lipid profiles and to provide guidance for the laboratory reporting of abnormal non-fasting or fasting lipid profiles.

Methods and results Extensive observational data, in which random non-fasting lipid profiles have been compared with those determined under fasting conditions, indicate that the maximal mean changes at 1–6 h after habitual meals are not clinically significant [+0.3 mmol/L (26 mg/dL) for triglycerides; −0.2 mmol/L (8 mg/dL) for total cholesterol; −0.2 mmol/L (8 mg/dL)

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for LDL cholesterol; +0.2 mmol/L (8 mg/dL) for calculated remnant cholesterol; −0.2 mmol/L (8 mg/dL) for calculated non-HDL cholesterol]; concentrations of HDL cholesterol, apolipoprotein A1, apolipoprotein B, and lipoprotein(a) are not affected by fasting/non-fasting status. In addition, non-fasting and fasting concentrations vary similarly over time and are comparable in the prediction of cardiovascular disease. To improve patient compliance with lipid testing, we therefore recommend the routine use of non-fasting lipid profiles, while fasting sampling may be considered when non-fasting triglycerides >5 mmol/L (440 mg/dL). For non-fasting samples, laboratory reports should flag abnormal concentrations as triglycerides ≥2 mmol/L (175 mg/dL), total cholesterol ≥5 mmol/L (190 mg/dL), LDL cholesterol ≥3 mmol/L (115 mg/dL), calculated remnant cholesterol ≥0.9 mmol/L (35 mg/dL), calculated non-HDL cholesterol ≥3.9 mmol/L (150 mg/dL), HDL cholesterol ≤1 mmol/L (40 mg/dL), apolipoprotein A1 ≤1.25 g/L (125 mg/dL), apolipoprotein B ≥1.0 g/L (100 mg/dL), and lipoprotein(a) ≥50 mg/dL (80th percentile); for fasting samples, abnormal concentrations correspond to triglycerides ≥1.7 mmol/L (150 mg/dL). Life-threatening concentrations require separate referral when triglycerides >10 mmol/L (880 mg/dL) for the risk of pancreatitis, LDL cholesterol >13 mmol/L (500 mg/dL) for homozygous familial hypercholesterolaemia, LDL cholesterol >5 mmol/L (190 mg/dL) for heterozygous familial hypercholesterolaemia, and lipoprotein(a) >150 mg/dL (99th percentile) for very high cardiovascular risk.

Conclusion We recommend that non-fasting blood samples be routinely used for the assessment of plasma lipid profiles. Laboratory reports should flag abnormal values on the basis of desirable concentration cut-points. Non-fasting and fasting measurements should be complementary but not mutually exclusive.

Keywords Lipids • Lipoproteins • Cardiovascular disease • Stroke • Reference values • Normal values

Introduction

Most individuals consume several meals during the day and some consume snacks between meals; the postprandial state therefore predominates over a 24 h period. Nonetheless, in clinical practice, the lipid profile is conventionally measured in blood plasma or serum obtained after fasting for at least 8 h, and therefore may not reflect the daily average plasma lipid and lipoprotein concentrations and associated risk of cardiovascular disease.[1,2]

Interestingly, evidence is lacking that fasting is superior to non-fasting when evaluating the lipid profile for cardiovascular risk assessment. However, there are advantages to using non-fasting samples rather than fasting samples for measuring the lipid profile.[3–7] Since 2009, non-fasting lipid testing has become the clinical standard in Denmark, based on recommendations from the Danish Society for Clinical Biochemistry that all laboratories in Denmark use random non-fasting lipid profiles as the standard, while offering clinicians the option of re-measuring triglyceride concentrations in the fasting state if non-fasting values are >4 mmol/L (350 mg/dL).[8,9] Furthermore, the UK NICE guidelines have endorsed non-fasting lipid testing in the primary prevention setting since 2014.[10]

The most obvious advantage of non-fasting rather than fasting lipid measurements is that it simplifies blood sampling for patients, laboratories, general practitioners, and hospital clinicians and is also likely to improve patient compliance with lipid testing.[3–7] Indeed, patients are often inconvenienced by having to return on a separate visit for a fasting lipid profile and may default on essential testing. Also, laboratories are burdened by a large volume of patients attending for tests in the morning. Finally, clinicians are burdened by having to review and make decisions on the findings in the lipid profile at a later date. This situation may also require an additional phone call, email, or even a follow-up clinic visit, placing extra workloads on busy clinical staff.

Perceived limitations to adopting non-fasting lipid measurements include the following: (i) fasting before a lipid profile measurement is believed to provide more standardized measurements; (ii) non-fasting lipid profiles are perceived as providing less accurate measurements and may make calculation of low-density lipoprotein (LDL) cholesterol via the Friedewald equation invalid; (iii) as fasting has been the clinical standard, it is unclear what values should be flagged as abnormal when using non-fasting rather than fasting plasma lipid profiles. These perceived limitations will be addressed in this paper.

The aims of the present joint consensus statement are to critically evaluate the use of non-fasting rather than fasting lipid profiles, and the clinical implications of this question with a view to providing appropriate guidance for laboratory and clinicians. Based on evidence from large-scale population studies and registries and on consensus of expert opinions, the European Atherosclerosis Society/European Federation of Clinical Chemistry and Laboratory Medicine (EAS/EFLM) joint consensus statement proposes recommendations on (i) situations when fasting is not required for a lipid profile and (ii) how laboratory reports should flag abnormal lipid profiles to improve compliance of patients and clinicians with concentration goals used in guidelines and consensus statements on cardiovascular

Table 1 Key recommendations

Fasting is not required routinely for assessing the plasma lipid profile
When non-fasting plasma triglyceride concentration >5 mmol/L (440 mg/dL), consideration should be given to repeating the lipid profile in the fasting state
Laboratory reports should flag abnormal values based on desirable concentration cut-points
Life-threatening or extremely high concentrations should trigger an immediate referral to a lipid clinic or to a physician with special interest in lipids

disease prevention.[11–15] This joint consensus statement is aimed at internists, general practitioners, paediatricians, cardiologists, endocrinologists, clinical biochemists, laboratory professionals, public health practitioners, health service planners, other health professionals, healthcare providers, and patients worldwide. Key recommendations are given in *Table 1*.

Constituents of the plasma lipid profile

A standard lipid profile includes measurements of plasma or serum concentrations of total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (*Figure 1*).

Total cholesterol, HDL cholesterol, and triglycerides are measured directly, while LDL cholesterol can either be measured directly or calculated by the Friedewald equation if triglycerides are <4.5 mmol/L (<400 mg/dL): total cholesterol minus HDL cholesterol minus triglycerides/2.2 (all in mmol/L; or minus triglycerides/5 with values in mg/dL),[16] with direct measurement of LDL cholesterol at triglyceride concentrations ≥4.5 mmol/L (400 mg/dL). Traditionally, the Friedewald equation has been applied to a fasting lipid profile; however, calculated LDL cholesterol determined with this equation at triglyceride concentrations <4.5 mmol/L (400 mg/dL) is similar to LDL cholesterol measured directly on both fasting and non-fasting lipid profiles (*Figure 2*).[17,18] These four measurements can, without additional cost, be supplemented with remnant cholesterol and non-HDL cholesterol.

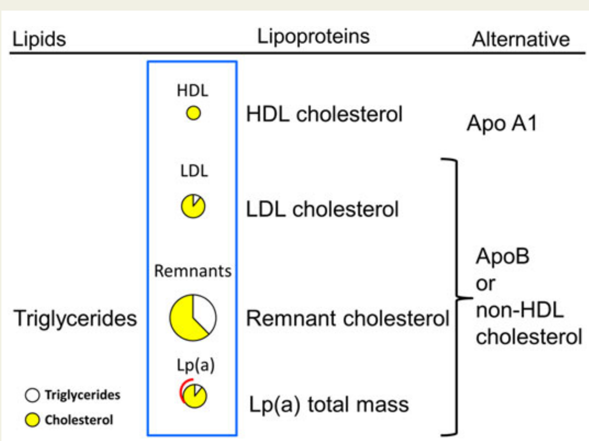

Figure 1 Lipids, lipoproteins, and apolipoproteins as part of standard and expanded lipid profiles. Standard lipid profiles consist of triglycerides and total, low-density lipoprotein, and high-density lipoprotein cholesterol; however, a standard lipid profile could also report calculated remnant cholesterol and calculated non-high-density lipoprotein cholesterol as these come at no additional cost. Calculated remnant cholesterol is non-fasting total cholesterol minus low-density lipoprotein cholesterol minus high-density lipoprotein cholesterol. Calculated non-high-density lipoprotein cholesterol is total cholesterol minus high-density lipoprotein cholesterol. Lipoprotein(a) should be measured at least once in every individual screened for cardiovascular risk in order to detect potentially high concentrations of this genetic risk factor. Finally, apolipoprotein B and apolipoprotein A1 can be used as alternatives to non-high-density lipoprotein and high-density lipoprotein cholesterol, but these measurements come at an extra cost. Figure designed by Prof. B.G. Nordestgaard.

Remnant cholesterol (=triglyceride-rich lipoprotein cholesterol) is calculated as total cholesterol minus LDL cholesterol minus HDL cholesterol, using non-fasting or fasting lipid profiles; if LDL cholesterol is also calculated, then remnant cholesterol is equivalent to triglycerides/2.2 in mmol/L and to triglycerides/5 in mg/dL. Calculated remnant cholesterol is a strong causal risk factor for cardiovascular disease.[19–21] Non-HDL cholesterol is calculated as total cholesterol minus HDL cholesterol and is equivalent to LDL cholesterol, remnant cholesterol and lipoprotein(a) cholesterol combined (*Figure 1*). The use of non-HDL cholesterol for cardiovascular disease risk prediction has been emphasized in several guidelines and consensus papers.[12–15]

The most important additional measurement for inclusion for cardiovascular disease risk prediction is lipoprotein(a) [Lp(a)]. This genetic, causal cardiovascular risk factor[11,22] should be measured at least once in all patients screened for cardiovascular risk;[11] it is noteworthy that Lp(a) concentrations vary little over time (<10%) in any individual. The determination of Lp(a) should not, however, be included in repeated lipid profile measurements in the same patient, unless therapeutic intervention is aimed at reducing Lp(a) concentrations or in selected circumstances. Importantly, the cholesterol content of Lp(a), corresponding to 30% of Lp(a) total mass,[23] is included in total, non-HDL, and LDL cholesterol values and its apolipoprotein B content in the apolipoprotein B value.

Finally, measurements of apolipoprotein B and apolipoprotein A1 can be used as alternatives to non-HDL and HDL cholesterol measurements, respectively (*Figure 1*),[13–15,24] but these determinations come at extra cost.

Why has fasting been the standard?

Venipuncture is a universal practice involved in testing the lipid profile with the purposes of predicting cardiovascular risk and/or monitoring responses to lipid-lowering therapy. Some guidelines continue to promulgate the conventional practice of measuring the lipid profile in the fasting state,[25] although other organizations endorse non-fasting lipid profiles.[8,10] The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines do not require fasting for atherosclerotic cardiovascular disease risk estimation; however, they do recommend a fasting lipid panel before statin initiation to calculate LDL cholesterol and for individuals with non-HDL cholesterol ≥5.7 mmol/L (220 mg/dL) or triglycerides ≥5.7 mmol/L (500 mg/dL), as these may be clues to genetic and/or secondary causes of hypertriglyceridaemia.[25] One reason among others for preferring fasting lipid profiles is the increase in triglyceride concentration seen during a fat tolerance test;[26,27] however, the increase in plasma triglycerides observed after habitual food intake in most individuals is much less than that observed during a fat tolerance test.[3,4,9,28–31] As a fast-food meal consisting of e.g. a burger, a shake, and fries might be considered a fat tolerance test, in areas where fast-food consumption is especially high patients may be advised to avoid high-fat, fast-food meals on the day of lipid profile testing. Also, as LDL cholesterol is often calculated by the Friedewald equation, which includes the triglyceride concentration,

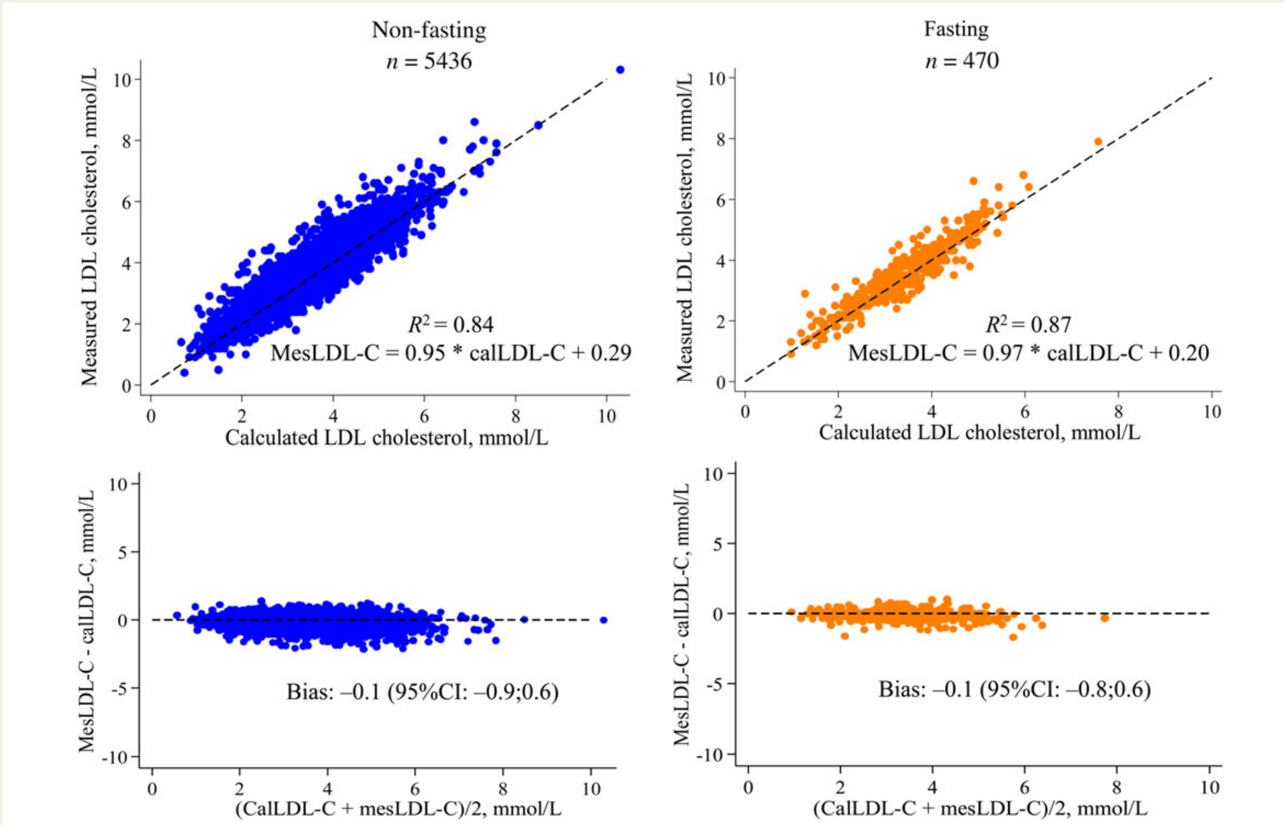

Figure 2 Comparison of calculated low-density lipoprotein cholesterol using the Friedewald equation with low-density lipoprotein cholesterol measured directly using random non-fasting and fasting lipid profiles. Only lipid profiles with triglycerides <4.5 mmol/L (400 mg/dL) were included, as low-density lipoprotein is typically measured using a direct low-density lipoprotein cholesterol assay when triglycerides are ≥4.5 mmol/L. Mes, measured; Cal, calculated using the Friedewald equation (low-density lipoprotein cholesterol = total cholesterol − high-density lipoprotein cholesterol − triglycerides/2.2; all values in mmol/L; if values are in mg/dL then use triglycerides/5). Figure designed by Prof. B.G. Nordestgaard and Dr A. Langsted based on unpublished data from individuals participating in the Copenhagen City Heat Study 2001–2003 examination.

calculated LDL cholesterol has been thought to be affected substantially by food intake; however, directly measured and calculated LDL cholesterol values are similar using both fasting and non-fasting lipid profiles (*Figure 2*).[17,18] If this Friedewald equation is employed, there may be some underestimation of LDL cholesterol when chylomicrons are present, which may even be circumvented if a modification of this equation is used.[32] Also, many randomized lipid-lowering trials have used fasting lipid measurements and, in order to follow evidence-based practice, fasting blood sampling has often been the standard in everyday risk assessment. However, numerous population-based studies and at least three major statin trials used random, non-fasting blood sampling (*Table 2*), providing a robust evidence base for a change in the conventional practice of using fasting samples.

Influence of food intake on the plasma lipid profile

Several large-scale, population-based studies and registries including children, women, men, and patients with diabetes have now established that plasma lipids and lipoproteins change only modestly in response to habitual food intake (*Figures 3* and *4*, *Table 3*);[3,4,9,29,30] this applies to the majority of individuals, but rarely some exhibit exaggerated responses. These studies were the Women's Health Study from the USA, the Copenhagen General Population Study from Denmark, the National Health and Nutrition Examination Survey from the USA (*Figure 3*), and the Calgary Laboratory Services from Canada (*Figure 4*). Among all studies comparing non-fasting with fasting lipid profiles, minor increases in plasma triglycerides and minor decreases in total and LDL cholesterol concentrations were observed, with no change in HDL cholesterol concentrations. These minor and transient changes in lipid concentrations appear to be clinically insignificant; however, Langsted *et al.* observed a transient drop in LDL cholesterol concentration of 0.6 mmol/L (23 mg/dL) at 1–3 h after a meal in diabetic patients, which could be of clinical significance,[33] particularly if this is used as an argument to withhold statins in a given patient. Of note, the reduction in total and LDL cholesterol at 1–3 h after the last meal observed in individuals with and without diabetes became statistically insignificant after adjusting for plasma albumin concentration as a marker of fluid intake;[3,9] therefore, such a drop in total and LDL cholesterol is

Table 2 **Population-based studies and statin trials that have employed non-fasting plasma lipid profiles to assess cardiovascular disease risk and trial outcomes, respectively**

Population-based studies totalling >300 000 non-fasting individuals	Statin trials totalling 43 000 non-fasting individuals
Tromsø Heart Study	Heart Protection Study
Norwegian National Health Service	Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm
British Population Studies	Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine
European Prospective Investigation of Cancer–Norfolk	
Northwick Park Heart Study	
Apolipoprotein-related Mortality Risk	
Copenhagen City Heart Study	
Women's Health Study	
Nurses' Health Study	
Physicians' Health Study	
National Health and Nutrition Examination Survey III	
Circulatory Risk in Communities Study	
Copenhagen General Population Study	
The global 52-country case-control INTERHEART study	

unrelated to food intake, noting that a similar drop may even be observed in a fasting lipid profile, since water intake is allowed *ad libitum* before a fasting blood test.[2] Thus, the only way to prevent this drop in LDL cholesterol concentrations using either fasting or non-fasting lipid profiles is to forbid water intake before lipid profiles testing, while so-called fasting sampling will not remove this phenomenon. Importantly, in patients with diabetes, a fasting lipid profile may further disguise postprandial triglyceride increases that may be particularly important in the diabetic state.

For the purpose of the present joint consensus statement, we updated the analyses of Langsted *et al.*[3,34] (*Figure 5*), based on the Copenhagen General Population Study and including 92 285 men and women from the Danish general population. As in previous reports (*Table 3*),[3,4,9,29,30,34] the maximal mean changes at 1–6 h after habitual meals were considered clinically insignificant at +0.3 mmol/L (26 mg/dL) for triglycerides, −0.2 mmol/L (8 mg/dL) for total cholesterol, −0.2 mmol/L (8 mg/dL) for LDL cholesterol, +0.2 mmol/L (8 mg/dL) for calculated remnant cholesterol, and −0.2 mmol/L (8 mg/dL) for calculated non-HDL cholesterol, while concentrations for HDL cholesterol, apolipoprotein A1, apolipoprotein B, and Lp(a) remained unchanged (*Figure 5*). Naturally, the corresponding changes in concentrations in individual patients will differ from the mean changes seen in *Table 3* and in *Figures 3–5*, exactly as concentrations will differ from one fasting measurement to another in the same individual.

Influence of food intake on the prediction of cardiovascular risk

We exist mostly in the non-fasting state, which therefore reflects our habitual physiological status. However, blood samples typically measured after an 8–12 h fast have been the standard for assessing the plasma lipid profile.[1,2] Postprandial effects do not appear to

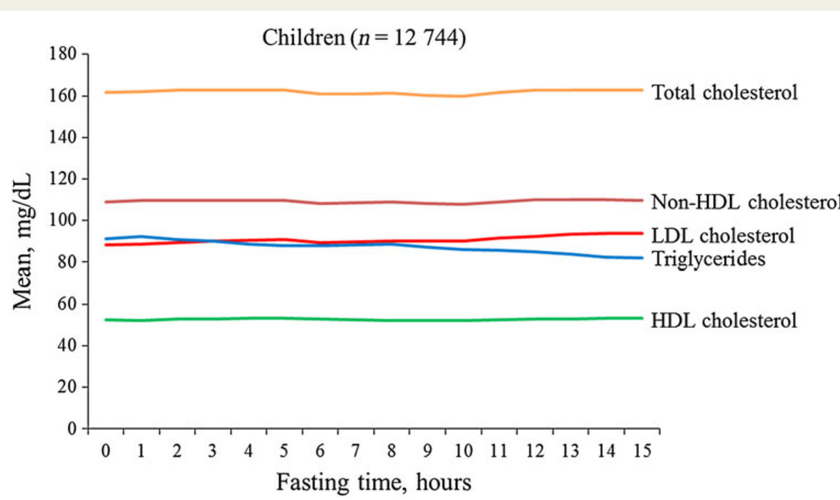

Figure 3 Mean concentrations of lipids and lipoproteins as a function of the fasting period following the last meal in children from the US general population. The last meal simply represents what the particular child chose to eat at that particular day before blood sampling, with no information or requirement on amount or type of food eaten. Based on 12 744 children from the National Health and Nutrition Examination Survey.[30]

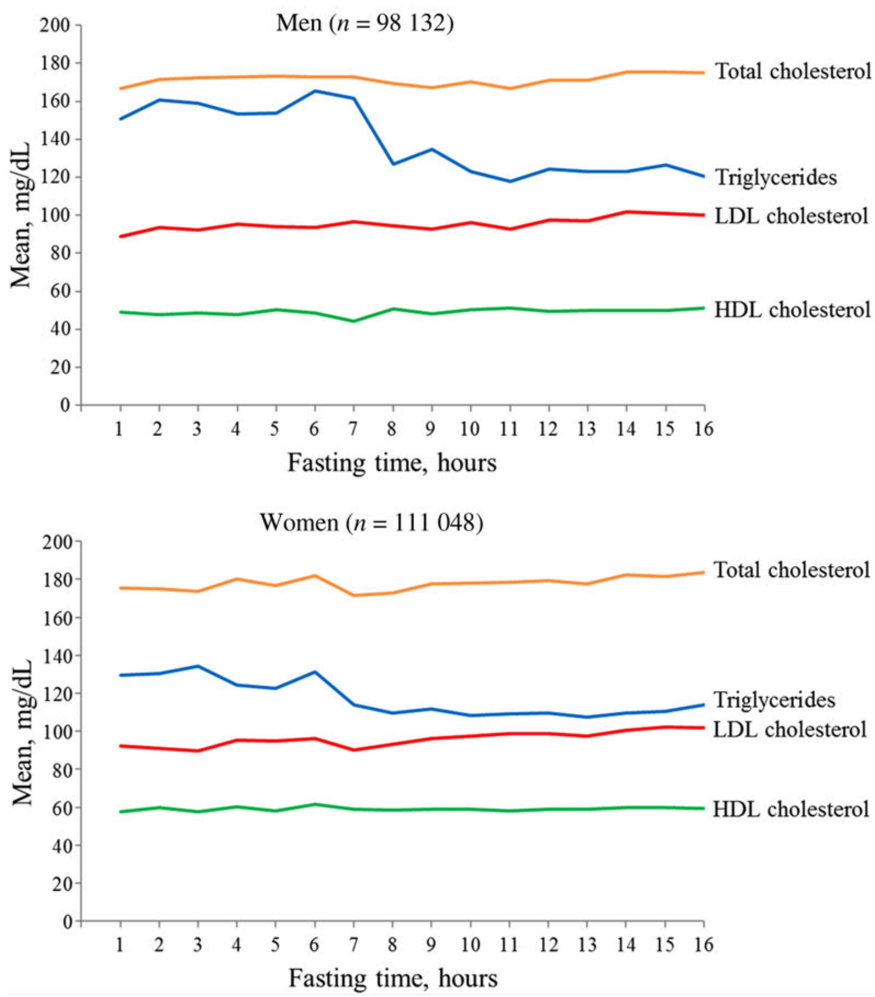

Figure 4 Mean concentrations of lipids and lipoproteins as a function of the period of fasting following the last meal in men and women from the Canadian general population. The last meal simply represents what the particular individual chose to eat at that particular day before blood sampling, with no information or requirement on amount or type of food eaten. Based on 209 180 men and women from Calgary Laboratory Services.[29]

diminish, and may in fact enhance, the strength of the associations between plasma lipid, lipoprotein, and apolipoprotein concentrations and risk of cardiovascular disease.

Since the 1970s, numerous reports from well-conducted, large, representative, and mostly prospective studies with medium- to long-term follow-up have consistently found that non-fasting lipids suffice for screening of cardiovascular disease risk.[3,4,31,35–39] These studies have examined clinical outcomes ranging from incident cardiovascular disease events (myocardial infarction, stroke, and revascularization) to cardiovascular or all-cause mortality, with consistent associations for non-fasting lipid profiles with cardiovascular disease risk. Furthermore, studies that included fasting and/or non-fasting individuals have found generally similar or sometimes superior cardiovascular disease risk associations for non-fasting compared with fasting lipid profiles, including for triglycerides;[3,4,31,38,39] the challenge of taking small amounts of alcohol during non-fasting hours of the day and its influence on lipid profile values has often not been studied. Prospective studies that have assessed non-fasting lipid profiles are shown in *Table 2*.

A meta-analysis from the Emerging Risk Factors Collaboration that analysed the association of lipid profiles and risk of coronary heart disease events from 68 prospective studies, and included over 300 000 individuals, equally found no attenuation of the strength of the association between plasma lipid and lipoprotein concentrations and incident cardiovascular events in the 20 studies that used non-fasting blood samples; indeed, non-fasting non-HDL cholesterol and non-fasting calculated LDL cholesterol were superior to fasting measurements for predicting cardiovascular risk ($n = 103\,354$; number of events 3829).[36] Furthermore, at least three large clinical trials of statin therapy (Heart Protection Study, Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm, and the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) involving nearly 43 000 participants used non-fasting lipid profile measurements (*Table 2*).

Table 3 Maximal mean changes in lipids and lipoproteins at 1–6 h after consumption of habitual meals as part of a standard lipid profile in individuals in large-scale population-based studies and registries

	Study population	Random non-fasting compared with fasting concentrations			
		Triglycerides	Total cholesterol	LDL cholesterol	HDL cholesterol
Mora et al. (2008)[4]	26 330 women from the Women's Health Study	↑ 0.2 mmol/L ↑ 18 mg/dL ↑ 16%	↓ 0.1 mmol/L ↓ 4 mg/dL ↓ 1%	↓ 0.2 mmol/L ↓ 8 mg/dL ↓ 5%	No change
Langsted et al. (2008)[3]	33 391 men and women from the Copenhagen General Population Study	↑ 0.3 mmol/L ↑ 26 mg/dL ↑ 21%	↓ 0.2 mmol/L[a] ↓ 8 mg/dL ↓ 4%	↓ 0.2 mmol/L[a] ↓ 8 mg/dL ↓ 6%	↓ 0.1 mmol/L ↓ 4 mg/dL ↓ 6%
Steiner et al. 2011[30]	12 744 children from the National Health and Nutrition Examination Survey	↑ 0.1 mmol/L ↑ 9 mg/dL ↑ 10%	↓ 0.1 mmol/L ↓ 4 mg/dL ↓ 2%	↓ 0.1 mmol/L ↓ 4 mg/dL ↓ 4%	No change
Langsted and Nordestgaard (2011)[9]	2270 men and women with diabetes from the Copenhagen General Population Study	↑ 0.2 mmol/L ↑ 18 mg/dL ↑ 11%	↓ 0.4 mmol/L[a] ↓ 15 mg/dL ↓ 8%	↓ 0.6 mmol/L[a] ↓ 23 mg/dL ↓ 25%[b]	No change
	56 164 men and women without diabetes from the Copenhagen General Population Study	↑ 0.2 mmol/L ↑ 18 mg/dL ↑ 14%	↓ 0.3 mmol/L[a] ↓ 12 mg/dL ↓ 5%	↓ 0.3 mmol/L[a] ↓ 12 mg/dL ↓ 9%	No change
Sidhu and Naugler (2012)[29]	209 180 men and women from Calgary Laboratory Services	↑ 0.3 mmol/L ↑ 26 mg/dL ↑ 21%	No change	↓ 0.1 mmol/L ↓ 4 mg/dL ↓ 4%	No change

Values in mmol/L were converted to mg/dL by multiplication with 38.6 for cholesterol and by 88 for triglycerides.
[a]No longer statistically significant after adjustment for reduction in plasma albumin concentrations; thus this drop in total and LDL cholesterol is due to fluid intake, not to food intake. In other words, as water intake is allowed during the up to 8 h fasting before lipid profile testing,[2] this reduction in total and LDL cholesterol will also occur for fasting lipid profiles.
[b]Langsted et al. observed a drop in LDL cholesterol of 0.6 mmol/L (23 mg/dL) at 1–3 h after a meal in diabetics, which could be of clinical significance,[33] particularly if this precluded initiation of statin therapy. However, such an LDL reduction may also occur for fasting lipid profiles with water intake allowed,[2] as the likely explanation for the LDL cholesterol drop is fluid intake and ensuing haemodilution.

Finally, for the purpose of this joint consensus statement and based on the Copenhagen General Population Study including 92 285 men and women from the Danish general population, we examined the risk of ischaemic heart disease and myocardial infarction for the highest vs. lowest quintile of random non-fasting lipids, lipoproteins, and apolipoproteins as part of standard and expanded lipid profiles (*Figure 6*); all lipids, lipoproteins, and apolipoproteins were associated strongly with the risk of both endpoints.

Hence, numerous prospective cohorts have found significant associations for non-fasting lipids, lipoproteins, and apolipoproteins with cardiovascular disease risk, and several landmark clinical trials of statin therapy have used non-fasting lipids for trial entry criteria and for monitoring the efficacy of lipid-lowering therapy. Collectively, these observations suggest that non-fasting blood sampling is highly effective, practical, and advantageous in assessing lipid-mediated cardiovascular disease risk and treatment responses.

Recommendations on the use of non-fasting lipid profiles

To improve patient compliance with lipid testing, we therefore recommend that non-fasting lipid profiles be used in the majority of patients (*Table 4*), while with non-fasting plasma triglyceride >5 mmol/L (440 mg/dL), fasting sampling may be considered. However, as lipid profile measurements often are taken repeatedly in the same patient, a single, spurious, non-fasting very high triglyceride concentration due to a very high fat intake preceding blood sampling will be followed by other measurements with lower concentrations.

Fasting can be a barrier to population screening, is unpopular with children, is often unsuitable for patients with diabetes, and counters the use of point-of-care testing, and fasting requirements can add to the overall costs of lipid testing. Non-fasting tests are also used to assess other metabolic disorders, such as haemoglobin A1c in diabetes. The collective sources of evidence reviewed above have therefore led to the notion that fasting samples are not essential for evaluation of cardiovascular risk.

Arguments against the use of non-fasting samples also merit consideration. There is evidence that the non-fasting condition may marginally lower plasma LDL cholesterol concentrations owing to liberal intake of fluids (*Table 3*), and therefore lead to a potential minor misclassification of cardiovascular risk, as well as to error in initiating or altering lipid-lowering medication; although not all studies agree, this risk is small and may chiefly apply to diabetic subjects.[5,9,33] While a non-fasting sample is sufficient to diagnose an isolated hypercholesterolaemia, such as familial hypercholesterolaemia, or elevated Lp(a), it can possibly confuse the distinction between familial hypercholesterolaemia and genetic forms of high triglycerides. Since non-fasting may therefore impair the accuracy

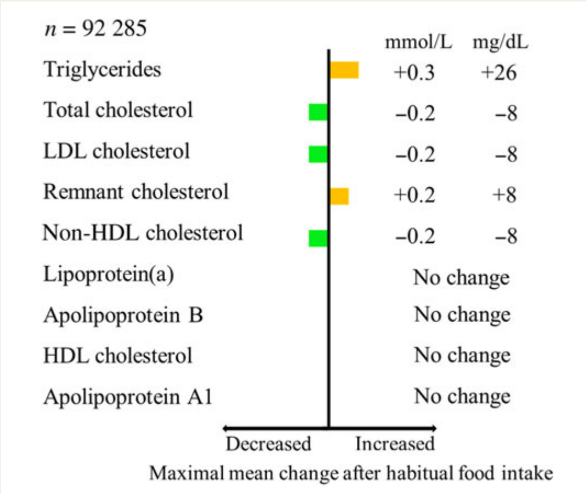

Figure 5 Maximal mean changes at 1–6 h after habitual food intake of lipids, lipoproteins, and apolipoproteins as part of standard and expanded lipid profiles in individuals in the Danish general population. Calculated remnant cholesterol is non-fasting total cholesterol minus low-density lipoprotein cholesterol minus high-density lipoprotein cholesterol. Calculated non-high-density lipoprotein cholesterol is total cholesterol minus high-density lipoprotein cholesterol. Adapted and updated from Langsted *et al.*,[3,34] based on 92 285 individuals from the Copenhagen General Population Study recruited in 2003 through 2014. Of all participants, 12% were receiving statins. Values in mmol/L were converted to mg/dL by multiplication with 38.6 for cholesterol and by 88 for triglycerides.

in diagnosing some forms of hyperlipidaemia, we recommend that laboratories should also offer measurement of fasting triglycerides according to clinical context and indications, as in the case of very high non-fasting triglyceride concentration. Plasma lipids can be highly variable in children and a precise diagnosis of a lipid disorder that requires drug therapy may necessitate at least a second sample in the fasting state. From an evidence-based perspective, fasting and non-fasting samples have never been tested head-to-head in a clinical trial to assess how the corresponding lipid profiles alter clinical management and the disposition of patients, and what the relative cost-effectiveness of both approaches is. It is most unlikely that such a study will ever be funded, however.

What pragmatic recommendations can be made? First, non-fasting and fasting measurements of the lipid profile must be viewed as complementary and not mutually exclusive (*Table 4*). Common sense must prevail and a distinction made between their use in screening, assessment, and diagnosis. Fasting is less critical for first-stage screening, but may be more important when trying to establish a phenotypic diagnosis of genetically determined dyslipidaemias. Further, one circumstance where fasting may be especially value is getting a baseline lipid determination for those about to start medications that cause severe hypertriglyceridaemia in a genetically predisposed individual. Noting that fasting triglycerides are elevated can thus be useful before, e.g. steroid, oestrogen, or retinoid acid therapy. Also, fasting lipids have been used to follow the course of those recovering from hypertriglyceridaemic pancreatitis. Nevertheless, non-fasting blood samples can routinely be used for assessment of plasma lipid profiles in most situations (*Table 4*).

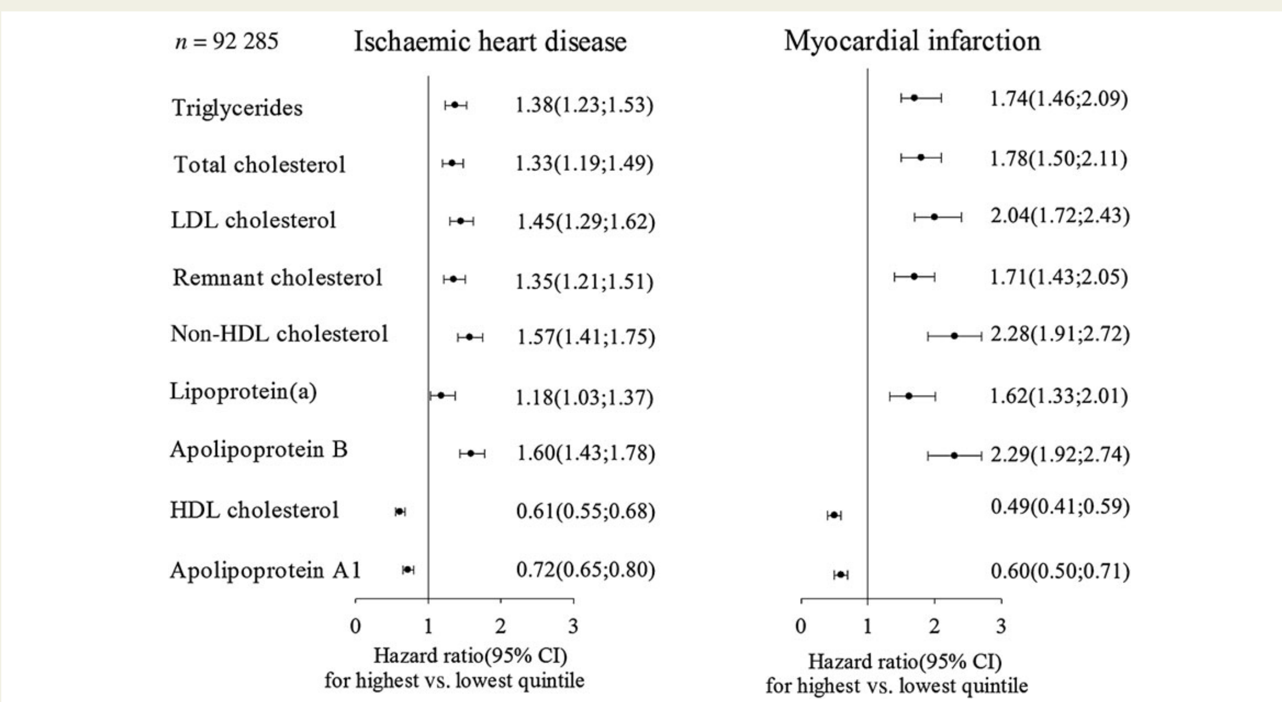

Figure 6 Risk of ischaemic heart disease and myocardial infarction for highest vs. lowest quintile of random non-fasting lipids, lipoproteins, and apolipoproteins as part of standard and expanded lipid profiles in individuals in the general population. Hazard ratios were adjusted for age, sex, smoking, hypertension, diabetes, and use of statins. Figure designed by Prof. B.G. Nordestgaard and Dr A. Langsted based on unpublished data on 92 285 individuals from the Copenhagen General Population Study recruited in 2003 through 2014. Of all participants, 12% were receiving statins. Maximal and median follow-up were 11 and 6 years, respectively.

Table 4 When to use non-fasting and fasting blood sampling to assess the plasma lipid profile

	Patients for lipid profile testing
Non-fasting	In most patients, including: • Initial lipid profile testing in any patient • For cardiovascular risk assessment • Patients admitted with acute coronary syndrome[a] • In children • If preferred by the patient • In diabetic patients[b] (due to hypoglycaemic risk) • In the elderly • Patients on stable drug therapy
Fasting	Can sometimes be required if: • Non-fasting triglycerides >5 mmol/L (440 mg/dL) • Known hypertriglyceridaemia followed in lipid clinic • Recovering from hypertriglyceridaemic pancreatitis • Starting medications that cause severe hypertriglyceridaemia • Additional laboratory tests are requested that require fasting[c] or morning samples (e.g. fasting glucose[c], therapeutic drug monitoring)

[a]Will need repeated lipid profile testing later because acute coronary syndrome lowers lipid concentrations.
[b]Diabetic hypertriglyceridaemia may be masked by fasting.
[c]In many countries, fasting blood sampling is restricted to very few analytes besides lipid profiles: one example is fasting glucose; however, in many countries, even fasting glucose measurement is being replaced by measurement of haemoglobin A1c without the need to fast.

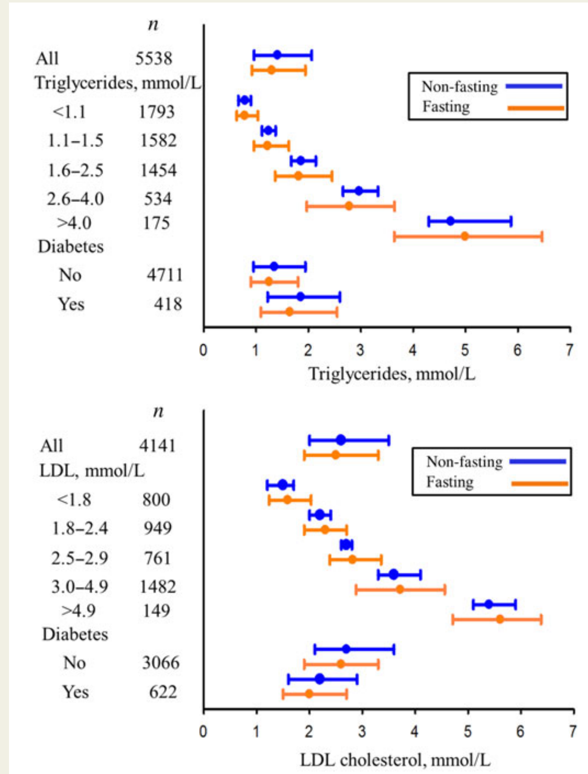

Figure 7 Comparison of concentrations of plasma triglycerides and low-density lipoprotein cholesterol measured in the non-fasting and fasting states in the same patients. Diabetes was determined as a haemoglobin A1c >7.1% (of all 5538 patients with both fasting and non-fasting triglyceride measurements, 371 did not have a haemoglobin A1c measurement). Values are medians and interquartile ranges; in strata of plasma triglycerides, the interquartile ranges are larger for fasting than for non-fasting values, which is explained by regression dilution bias as the groups were defined initially based on the non-fasting measurements. Figure designed by Prof. B.G. Nordestgaard and Dr A. Langsted based on unpublished data on patients from Herlev and Gentofte Hospital, Copenhagen University Hospital in the period 2011 through 2015.

Potential for risk misclassification

It is important to consider whether transferring from fasting to non-fasting lipid profiles could lead to misclassification of cardiovascular risk and error in initiating statin therapy. Importantly, since statin treatment is decided on the basis of an individual's global cardiovascular risk, including the presence of cardiovascular disease, familial hypercholesterolaemia and diabetes, and not just on plasma lipid values in both European and US guidelines,[15,25] minor changes in the lipid profile from fasting to non-fasting conditions (*Figures 3–5*, *Table 3*) will affect only a few individuals regarding the decision to start a statin or not. However, most guidelines use LDL cholesterol to monitor pharmacological treatment and as goals for treatment. In individuals with borderline LDL cholesterol, the lower LDL cholesterol observed 1–6 h after a habitual meal, particularly in diabetic patients (*Table 3*), needs to be considered when using non-fasting lipid profiles to decide whether to commence a statin or titrate its dose. Of note, since the observed reduction in LDL cholesterol is due to liberal fluid intake and haemodilution rather than to food consumption, a similar LDL reduction is likely to occur when using fasting lipid profiles with no restrictions on water intake.[2]

Novel findings from experience in Denmark

In 2009, the Danish Society for Clinical Biochemistry recommended that all laboratories in Denmark use random non-fasting lipid profile measurements rather than fasting profiles.[8,9] It was believed that a single spurious, non-fasting very high triglyceride concentration due to high fat intake preceding blood sampling would be followed by other measurements with lower concentrations. However, it was also recommended that laboratories should offer the option of re-measurement of triglyceride concentrations in the fasting state, if non-fasting triglyceride values were at >4 mmol/L (>350 mg/dL).

This change in blood sampling was easy to implement in Denmark: after adoption of the non-fasting strategy by major university hospitals in Copenhagen and subsequent corresponding reports in written and electronic media nationwide, patients and clinicians in the entire country pushed for similar changes at their local clinical biochemical laboratory. Only a few laboratories refused initially to follow this new practice, but by 2015 practically all laboratories in Denmark use non-fasting lipid profiles.

To illustrate the consequences of implementing this new blood sampling policy and for the purpose of the present joint consensus statement, we retrieved results for all triglyceride measurements at Herlev Hospital, Copenhagen University Hospital in the period April 2011 through April 2015: of ~60 000 triglyceride measurements, only 10% were measured in the fasting state. Further, among the 5538 patients with both a non-fasting and a fasting triglyceride measurement, concentrations were very similar fasting and non-fasting measures overall as well as when stratified by triglyceride concentrations and the presence or absence of diabetes (*Figure 7*, top). In groups stratified for triglyceride concentrations, the interquartile ranges were wider for fasting than for non-fasting triglycerides, which is explained by regression dilution bias as the initial groups were made based on non-fasting concentrations and then fasting concentrations were compared afterwards. Thus, if groups were made initially based on fasting concentrations, then the confidence intervals for non-fasting triglycerides were wider than for fasting triglycerides (data not shown). In other words, the variation in fasting and non-fasting triglyceride concentrations measured in the same individuals at two different occasions is similar, as is also clear for the value in all 5538 individuals combined (*Figure 7*, top). Results were also similar for LDL cholesterol comparing non-fasting and fasting values (*Figure 7*, bottom).

Recommendations on laboratory reporting of abnormal non-fasting and fasting lipid profiles

We recommend that laboratory reports should flag abnormal values based on desirable concentration cut-points, defined by guidelines and consensus statements,[11–15] and for non-fasting samples, flag abnormal concentrations as triglycerides ≥2 mmol/L (175 mg/dL)[40,41] (corrected for endogenous glycerol), total cholesterol ≥5 mmol/L (190 mg/dL), LDL cholesterol ≥3 mmol/L (115 mg/dL), calculated remnant cholesterol ≥0.9 mmol/L (35 mg/dL), calculated non-HDL cholesterol ≥3.9 mmol/L (155 mg/dL), HDL cholesterol ≤1 mmol/L (40 mg/dL) (sex-specific cut-points can be used for HDL cholesterol), apolipoprotein A1 ≤1.25 g/L (125 mg/dL), apolipoprotein B ≥1.0 g/L (100 mg/dL), and Lp(a) ≥50 mg/dL (80th percentile) (*Table 5*); for fasting samples, abnormal concentrations should be triglycerides ≥1.7 mmol/L (150 mg/dL), remnant cholesterol ≥0.8 mmol/L (30 mg/dL), and non-HDL cholesterol ≥3.8 mmol/L (145 mg/dL) while other measurements should use identical cut-points as for non-fasting values.

The majority of these cut-points correspond to desirable concentrations from guidelines and consensus statements.[11–15] However, a desirable concentration cut-point for non-fasting triglycerides has

Table 5 Abnormal plasma lipid, lipoprotein, and apolipoprotein concentration values that should be flagged in laboratory reports based on desirable concentration cut-points

Abnormal concentrations	Non-fasting			Fasting		
	mmol/L	mg/dL[a]	g/L	mmol/L	mg/dL[a]	g/L
Triglycerides[b]	≥2	≥175	≥1.75	≥1.7	≥150	≥1.50
Total cholesterol	≥5	≥190	≥1.90	≥5	≥190	≥1.90
LDL cholesterol	≥3	≥115	≥1.15	≥3	≥115	≥1.15
Remnant cholesterol[c]	≥0.9	≥35	≥0.35	≥0.8	≥30	≥0.30
Non-HDL cholesterol[d]	≥3.9	≥150	≥1.50	≥3.8	≥145	≥1.45
Lipoprotein(a)	[e]	≥50[f]	≥0.50	[e]	≥50[f]	≥0.50
Apolipoprotein B		≥100	≥1.00		≥100	≥1.00
HDL cholesterol[g]	≤1	≤40	≤0.40	≤1	≤40	≤0.40
Apolipoprotein A1		≤125	≤1.25		≤125	≤1.25

These values for flagging in laboratory reports are in some instances higher than corresponding to recommended desirable values in high and very high risk patients (*Tables 6* and *7*). We recommend to use SI units (e.g. mmol/L for lipids and g/L for apolipoproteins); however, as these values are not used in all countries, we also provide cut-points for other commonly used units.

LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very low-density lipoprotein; IDL, intermediate-density lipoprotein.

[a]Values in mmol/L were converted to mg/dL by multiplication with 38.6 for cholesterol and by 88 for triglycerides, followed by rounding to nearest 5 mg/dL; for total cholesterol, we used 5 mmol/L and 190 mg/dL, as these are the two desirable concentration cut-point typically used in guidelines.

[b]Triglyceride cut-points based on assays with correction for endogenous glycerol. In most laboratories, however, triglycerides are measured without subtraction of the glycerol blank; thus, triglycerides may wrongly be flagged as abnormal in rare individuals with very high plasma glycerol. That said, not accounting for the glycerol blank in outpatients rarely affected the triglyceride concentration >0.1 mmol/L; in inpatients, the effect was rarely over 0.28 mmol/L.[48] High endogenous glycerol is seen e.g. during intravenous lipid or heparin infusion.

[c]Calculated as total cholesterol minus LDL cholesterol minus HDL cholesterol, that is, VLDL, IDL, and chylomicron remnants in the non-fasting state and VLDL and IDL in the fasting state.

[d]Calculated as total cholesterol minus HDL cholesterol.

[e]There is no consensus on which cut-point value in mmol/L that should be used for lipoprotein(a).

[f]Value for lipoprotein(a) should represent ≥80th percentile of the specific lipoprotein(a) assay.

[g]Sex-specific cut-points can be used for HDL cholesterol.

Table 6 Treatment goals for prevention of cardiovascular disease according to current European Atherosclerosis Society/European Society of Cardiology guidelines[13]

Cardiovascular disease risk	LDL cholesterol		Non-HDL cholesterol		Apolipoprotein B	
	mmol/L	mg/dL	mmol/L	mg/dL	mg/dL	g/L
Very high	<1.8	<70	<2.6	<100	<80	<0.8
High	<2.5	<100	<3.3	<125	<100	<1.0
Moderate	<3.0	<115	<3.8	<145		

Table 7 Definition of hypertriglyceridaemia by European Atherosclerosis Society consensus statement[24]

Severe hypertriglyceridaemia	>10 mmol/L	>880 mg/dL
Mild-to-moderate hypertriglyceridaemia	2–10 mmol/L	180–880 mg/dL

been documented only recently;[40,41] we therefore choose to recommend flagging of abnormal concentrations of non-fasting triglycerides as ≥2 mmol/L (175 mg/dL), according to the recent study from the Women's Health Study that found that this cut-point was optimal for cardiovascular risk prediction. Interestingly, this is almost identical to the cut-points previously suggested by the EAS and by the Athens Expert Panel.[12,24,42] A concentration cut-point for fasting triglycerides at 1.7 mmol/L (150 mg/dL) was taken as 0.3 mmol/L lower than for non-fasting triglycerides, corresponding to the mean maximal increase of triglycerides following habitual food intake (*Figure 5*, *Table 3*). Interestingly, this cut-point is identical to those proposed previously for fasting triglycerides by the AHA[14] and the EAS.[12]

Usually, in laboratory medicine, results of measured parameters are considered to be abnormal if they exceed the age- and sex-specific reference interval (=2.5th to 97.5th percentiles). All results below or above these recommended cut-points are flagged with a character to show at a glance that this value deserves attention. Also automatic validation and flagging are used in many laboratories. Depending on the laboratory, this labelling can vary. Theoretically, the reference intervals should be established by each laboratory, but in most cases they are taken over from the general information provided by the manufacturer in the package insert. Due to wide-spread unhealthy life style, in most populations the upper reference cut-point (i.e. 97.5th percentiles) of total cholesterol (>7.8 mmol/L in Denmark) and LDL cholesterol (>5.5 mmol/L) as well as triglycerides (>4.4 mmol/L) are very high and place individuals at considerably increased cardiovascular risk. Therefore, flagging abnormal values based on desirable concentration cut-points rather than reference intervals are recommended to identify abnormal test results. Especially for LDL cholesterol, the desirable values vary with the individual's global risk between <1.8 mmol/L (70 mg/dL) (very high risk), <2.5 mmol/L (100 mg/dL) (high risk), and <3.0 mmol/L (115 mg/dL) (moderate risk)[15,25] (*Tables 6* and *7*). These different values are classified according to the presence or absence of co-morbidities (atherosclerotic cardiovascular disease, diabetes, chronic kidney disease) and other risk factors (age, gender, hypertension, smoking). This personalized reporting of desirable values is difficult to implement in laboratory reports because usually the clinical conditions and risk factors of the individual patient are not known to the laboratory professional. We therefore propose a simplified system of flagging abnormal values based on desirable concentration cut-points for moderate risk only, which may be complemented by more detailed information on risk stratified cut-offs in footnotes on the laboratory report or by references to web-based information of the same laboratory. Using such flagging emphasizes the importance of harmonization and standardization in laboratory medicine, and the responsibility of EAS and EFLM to communicate to laboratories when updates of cut-points are necessary as guidelines for cardiovascular disease prevention are revised.

According to the flagging of abnormal values based on desirable concentration cut-points proposed in *Table 5*, the following percentages of adults in the general population of a typical Western or Northern European country will have flagged test results in non-fasting lipid profiles: 27% will have triglycerides ≥2 mmol/L (175 mg/dL), 72% total cholesterol ≥5 mmol/L (190 mg/dL), 60% LDL cholesterol ≥3 mmol/L (115 mg/dL), 27% calculated remnant cholesterol ≥0.9 mmol/L (35 mg/dL), 50% calculated non-HDL cholesterol ≥3.9 mmol/L (150 mg/dL), 20% Lp(a) ≥50 mg/dL (80th percentile), 59% apolipoprotein B ≥1.0 g/L (100 mg/dL), 10% HDL cholesterol ≤1 mmol/L (40 mg/dL), and 9% will have apolipoprotein A1 ≤1.25 g/L (125 mg/dL) (*Figure 8*).

Life-threatening plasma lipid concentrations—what to do?

Life-threatening or extremely abnormal test results deserve special attention and reactions of the clinical biochemical laboratory. In this regard, the following extreme hyperlipidaemias should be noted: triglycerides >10 mmol/L (880 mg/dL) because of risk of acute pancreatitis,[24] LDL cholesterol >5 mmol/L (190 mg/dL) in adults or >4 mmol/L (155 mg/dL) in children and particularly >13 mmol/L (500 mg/dL) because of suspicious heterozygous and homozygous familial hypercholesterolaemia,[43–45] respectively, and Lp(a) >150 mg/dL (99th percentile) for very high risk of myocardial infarction and aortic valve stenosis[11,46,47] (*Table 8*). As such concentrations are always much above a common decision cut-point,

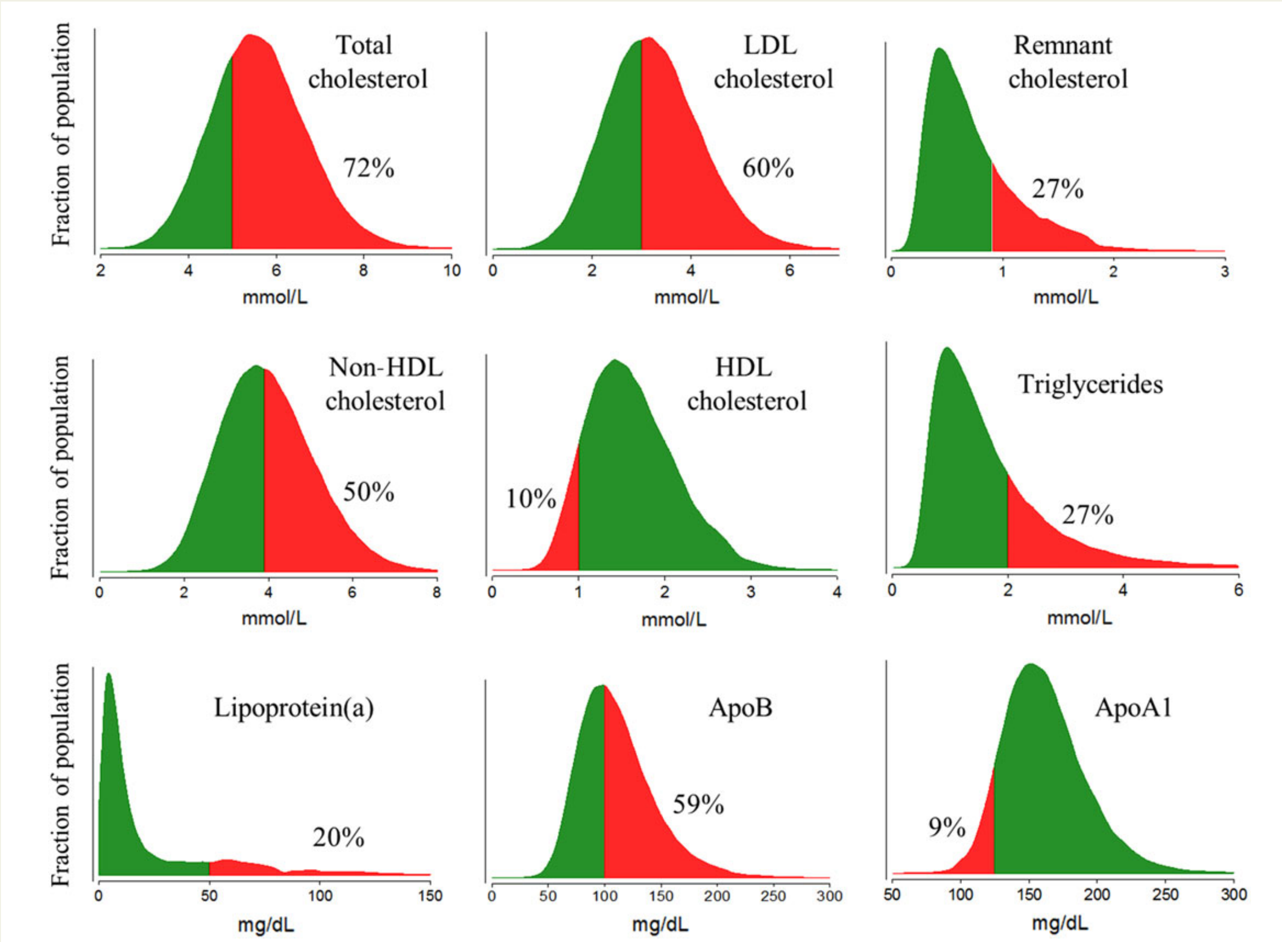

Figure 8 Proportion of non-fasting individuals in the general population with flagged abnormal concentrations in laboratory reports using desirable concentration cut-points as shown in *Table 5*. Of all participants, 12% were receiving statins. Figure designed by Prof. B.G. Nordestgaard and Dr A. Langsted based on unpublished data on 92 285 non-fasting individuals from the Copenhagen General Population Study recruited in 2003 through 2014.

Table 8 Life-threatening and extremely abnormal concentrations with separate reporting and consequent direct referral to a lipid clinic or to a physician with special interest in lipids

	Life-threatening concentrations	Refer patient to a lipid clinic or to a physician with special interest in lipids for further assessment of the following conditions
Triglycerides	>10 mmol/L >880 mg/dL[a]	Chylomicronaemia syndrome with high risk of acute pancreatitis[24]
LDL cholesterol	>13 mmol/L >500 mg/dL[a]	Homozygous familial hypercholesterolaemia with extremely high cardiovascular risk[44]
LDL cholesterol	>5 mmol/L >190 mg/dL[a]	Heterozygous familial hypercholesterolaemia with high cardiovascular risk[43]
LDL cholesterol in children	>4 mmol/L >155 mg/dL[a]	Heterozygous familial hypercholesterolaemia with high cardiovascular risk[45]
Lipoprotein(a)	>150 mg/dL >99th percentile	Very high cardiovascular risk, i.e for myocardial infarction and aortic valve stenosis[11,46,47]
LDL cholesterol Apolipoprotein B	<0.3 mmol/L <10 mg/dL	Genetic abetalipoproteinaemia
HDL cholesterol Apolipoprotein A1	<0.2 mmol/L <10 mg/dL	Genetic hypoalphalipoproteinaemia (e.g. lecithin cholesterol acyltransferase deficiency)

[a]Values in mmol/L were converted to mg/dL by multiplication with 38.6 for cholesterol and by 88 for triglycerides, followed by rounding to nearest 5 mg/dL.

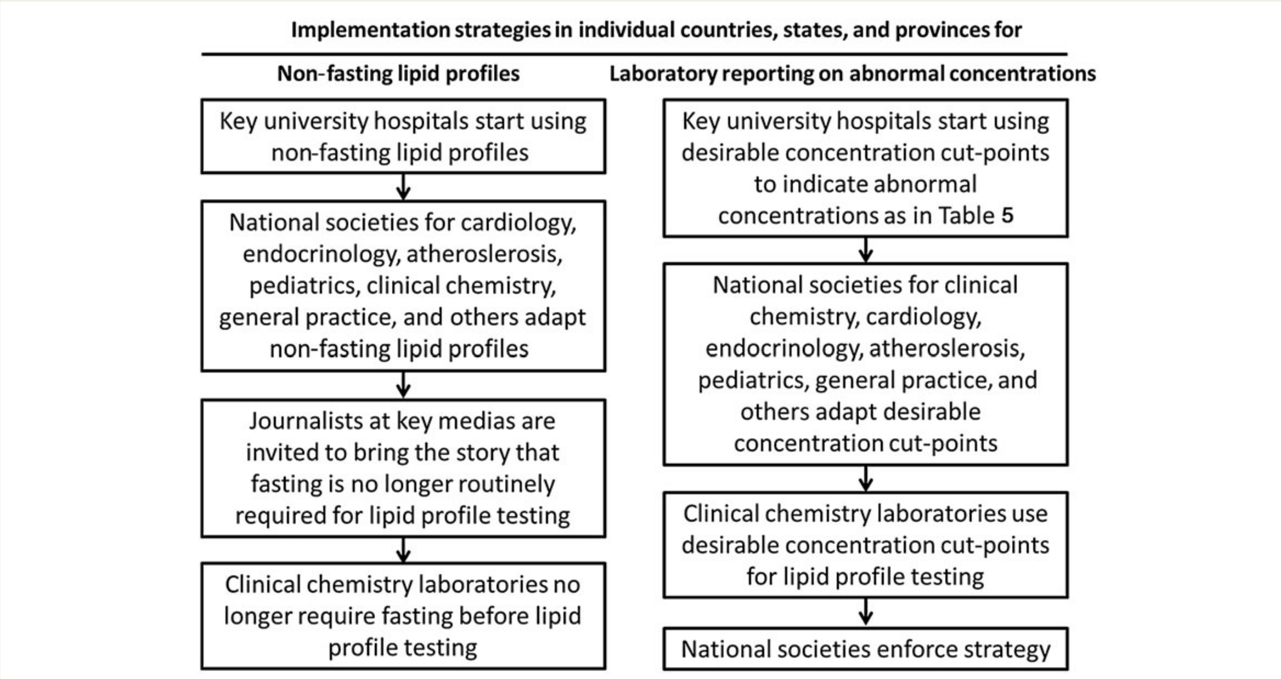

Figure 9 Suggested implementation strategies in individual countries, states, and/or provinces for use of non-fasting lipid profiles and for flagging in laboratory reports of abnormal values based on desirable concentration cut-points.

they should be flagged with special symbols to quickly initiate further diagnostic and possibly therapeutic actions, preferably with direct referral to a lipid clinic or to a physician with special interest in lipids. It is also important to refer patients with very low concentrations of LDL cholesterol, apolipoprotein B, HDL cholesterol, or apolipoprotein A1 to a specialist lipid clinic for further evaluation of a major monogenic disorder of lipid metabolism (*Table 8*).

Implementation of recommendations

Each country, state, and/or province in individual countries should adopt strategies for implementing routine use of non-fasting rather than fasting lipid profiles as well as flagging of abnormal values based on desirable concentration cut-points rather than using traditional reference intervals. Ideally, there should be one standard for reporting lipid profiles in each country as also accreditation bodies should be aware of the present consensus statement. *Figure 9* suggests implementation strategies; however, the strategy might differ from country to country based on existing local practice in relation to use of non-fasting lipid profiles and flagging of abnormal values based on desirable concentration cut-points used for assessing cardiovascular risk, making diagnoses, and for initiating lipid-lowering drug therapy. Finally, within countries with differing ethnic groups, the policy on non-fasting might need to be further refined. Indeed, e.g. individuals of South Asian or Latin American descent are more likely to have severe triglyceride elevations when compared with individuals of non-Hispanic white and black descent. This could be another reason to have a caveat about avoiding a high-fat, fast-food meal on the day of lipid profile testing.

Authors' contributions

EAS/EFLM Joint Consensus Panel members were nominated by EAS, EFLM, and the Co-chairs B.G.N. and M.L., to represent expertise across clinical and laboratory management and research in lipids from across the world. The Panel met twice, organized and chaired by M.L. and B.G.N. The first meeting critically reviewed the literature while the second meeting reviewed additional literature and scrutinized the first draft of the joint consensus statement. All Panel members agreed to conception and design, contributed to interpretation of available data, suggested revisions for this document, and approved the final document before submission.

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