Serum Lipid Levels and the Prevalence of Dyslipidaemia among Rural and Urban Thai Adults - are the NCEP III Guidelines Appropriate?

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The authors' objective was to describe the distribution of serum lipids and the prevalence of dyslipidaemia using US lipid-lowering guidelines in an adult Thai population. Fasting serum lipids were measured in a population-based survey that included 5305 rural and urban Thai adults aged 35 years. The US National Cholesterol Education Program (NCEP) guidelines were used to determine the eligibility of each individual for lipid-lowering therapy. Compared with urban residents, rural residents had lower mean levels of total cholesterol (men: 4.80 vs 5.54 mmol/L, women: 5.18 vs 5.71 mmol/L, both p < 0.001) and high density lipoprotein cholesterol (men: 1.06 vs 1.19 mmol/L, women: 1.13 vs 1.34 mmol/L, both p < 0.001). Mean triglyceride levels were higher in rural compared to urban populations, for both men (2.15 vs 1.88 mmol/L, p = 0.001) and women (1.73 vs 1.51 mmol/L, p = 0.01). Direct application of the NCEP guidelines identified up to 37% of the adult population (or 10 million adult Thais) as eligible for lipid-lowering drug therapy, which is an unfeasibly high proportion of the population. Urgent strategies are required to prevent increasing levels of dyslipidaemia in Thailand, as well as to develop and promulgate treatment guidelines that incorporate locally-relevant risk prediction functions.

Keywords: Lipids, Cholesterol, Triglycerides, Cardiovascular risk factors, Lipid-lowering guidelines, Thailand

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Thailand is a country in the midst of an epidemiologic transition. Coronary heart disease has been the leading cause of death in Thailand since 1989, and mortality rates from coronary disease continue to rise⁽¹⁾. In 1998 cardiovascular diseases accounted for about 17% of the estimated 318 000 deaths in Thailand⁽²⁾. The likely reasons for the emergence of chronic noncommunicable diseases are many, but include the marked, ongoing aging and urbanisation of the Thai population^(1,3).

Serum lipids are important determinants of cardiovascular risk. Behaviours associated with urbanisation, such as increased saturated fat consumption and decreased physical activity have been well described, and are associated with adverse changes in the lipid profile⁽⁴⁻⁶⁾. The importance of lipids and the benefits of cholesterol lowering have been acknow-ledged in a number of different treatment recommendations, including the recent third report of the US National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP III)⁽⁷⁾. In the absence of local guidelines, US recommendations are frequently used by physicians in Thailand to guide drug management in their patients. Whether this practice is appropriate and/or affordable is unclear.

The International Collaborative Study of Cardiovascular Diseases in Asia (InterASIA) was designed to provide reliable estimates of the prevalence of cardiovascular risk factors, including serum lipids, in a representative sample of the adult Thai and Chi-

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nese populations aged 35 years and over. In the present report the authors' describe the population distribution of serum lipid values in Thailand, with a particular emphasis on rural and urban differences. The authors' further investigated the implications of current "Western" lipid-lowering treatment recommendations for the prevention of cardiovascular diseases when applied to Thailand.

Material and Method

The design of the InterASIA study has been described in detail elsewhere⁽⁸⁾. Briefly, the present study utilised a complex sample survey design based on random sampling of individuals within representative enumeration districts (ED) in undeveloped, developing and developed rural regions, and slum and non-slum urban regions of Thailand. Each ED was based on city blocks and villages, in urban and rural areas respectively. Within each ED, and using local government registers of households, the population aged 35 years and over was stratified into eight demographic groups, defined by age (35-44, 45-54, 55-64 and > 65 years) and sex. Individuals were then sampled at random from each demographic group with the goal of recruiting a similar number of participants from each, but selecting no more than one individual from any household. All participants provided written, informed consent.

Data collection and measurements

Trained study staff administered a structured questionnaire, performed a brief physical examination and collected a fasting blood sample from each participant. The questionnaire sought information about basic socio-demographic variables, cardiovascular risk factors, history of cardiovascular diseases, current treatments, and behavioural characteristics. The physical examination included three measurements of blood pressure, and a standard anthropometric assessment (height, weight, waist and hip circumference).

Biochemical analysis was performed on venous samples obtained after an 8-hour overnight fast. Samples were stored immediately on ice, and centrifuged and separated on the day of collection. Sera were subsequently frozen and transported on dry ice to a central laboratory (Faculty of Medicine, Ramathibodi Hospital, Bangkok), where they were stored at -70 C until analysed using the Dimension RxLHM clinical chemistry system (Dade Behring Inc, Newark, USA). Serum total cholesterol (TC) and triglycerides (TG) were measured using enzymatic methods, while a homogenous method was used to assay high-density lipoprotein cholesterol (HDL-C). Low-density lipoprotein cholesterol (LDL-C) was calculated using Friedewald's method for those individuals with a triglyceride level \leq 4.4 mmol/L⁽⁹⁾. The central laboratory was standardised according to the criteria of the US Centers for Disease Control - National Heart Lung and Blood Institute Lipid Standardization Program⁽¹⁰⁾.

Defining eligibility for cholesterol-lowering treatment

After exclusion of the few participants with a known history of myocardial infarction, stroke, heart failure or peripheral vascular disease, the NCEP-ATP III guidelines were used to identify proportions and absolute numbers of adults aged 35 years and over in rural and urban Thailand who would qualify for lipid lowering drug therapy for primary prevention of coronary heart disease. The NCEP-ATP III treatment recommendations were based on risk stratification (using the number of cardiovascular risk factors, and a modified Framingham risk function to determine 10-year risk of developing coronary heart disease), and LDL-C levels (Table 1).

Statistical method

The STATA 8.0 statistical software package (StataCorp, College Station, TX, USA) was used to estimate population risk factor levels taking appropriate account of the complex survey design, using weights derived from the 2000 Thai National Census⁽³⁾. Estimates (with standard errors) of mean levels or proportions for lipid parameters and other risk factors were calculated for each age, sex and rural/urban subgroup in the Thai population. Comparison of risk factor levels between population subgroups were performed using t-tests for continuous variables (after log-transformation of triglycerides data to improve approximation to a normal distribution), and C² tests for categorical variables.

Results

Data from a total of 5305 participants were collected between May and October 2000. The overall response rate was 68%, and was higher in rural than urban regions (81 vs 61%, p < 0.001), and among females more than males (77 vs 57%, p < 0.001), but did not differ significantly by age group. Adequate questionnaire, blood pressure and anthropometric data were available from all but 53 (1%) participants, while a usable blood sample was available for 5111 (96%) of respondents.

Population distribution of lipid levels

The estimated mean (SE) value of serum TC for the entire adult Thai population was 5.03 (0.09) mmol/L in men, and 5.35 (0.07) mmol/L in women. The mean values for HDL-C and TC/HDL-C ratio were 1.10 (0.02) mmol/L and 4.79 (0.05) in men, and 1.20 (0.02) mmol/L and 4.68 (0.06) in women, respectively. Among men, the mean serum TG level was 2.07 (0.06) mmol/L, while the corresponding value among women was 1.66 (0.06) mmol/L.

Rural-urban differences in lipids

The mean values for TC, LDL-C, HDL-C, TC/ HDL-C ratio and TG in rural and urban populations are summarised in Table 2. For both men and women, TC and LDL-C was lower in rural areas compared with urban regions (both p < 0.001). Serum HDL-C was also lower in the rural population compared with urban residents for both sexes (both, p < 0.001). There was no significant difference in TC/HDL-C ratio in rural areas compared with urban areas for men (4.74 vs 4.89, p =0.16), while among women a higher mean ratio was observed among rural residents, although this difference was of borderline statistical significance (4.77 vs 4.49, p = 0.05). The estimated mean level of serum TG was significantly greater in rural areas than in the urban population, for men (p = 0.001) and for women (p = 0.01).

Variation in sex differences between the rural and urban populations was also observed for TC, LDL-C and the TC/HDL-C ratio (Table 2). Among rural residents, women had significantly higher values of TC than men (p < 0.001), while there was no significant

Table 1.	NCEP III	Treatment I	Recommendations

difference in TC between men and women in the urban population (p = 0.20). A similar pattern was observed for LDL-C. Within urban regions, the TC/HDL-C ratio was significantly greater in men compared with women (p = 0.003), however, there was no sex difference in the ratio among rural participants (p = 0.77). In both rural and urban regions, HDL-C was significantly higher in women than men (p = 0.02 for rural, p < 0.001 for urban). Similarly, the mean TG value was greater in men compared with women for both regions (both p < 0.001).

Other cardiovascular risk factors

Participants from rural areas had significantly lower mean levels of systolic and diastolic blood pressure, body mass index, and waist circumference (all p < 0.001) (Table 3). The prevalence of diabetes (known and newly-diagnosed) was also lower in rural regions (p = 0.02).

Eligibility for cholesterol-lowering treatment

After excluding 1.1% of the rural participants and 2.0% of the urban participants with a known history of vascular disease, the proportion and absolute numbers of Thai adults aged \geq 35 years that would qualify for lipid-lowering drug therapy under NCEP-ATP III primary prevention guidelines are shown in Fig. 1. Overall, under liberal "drug-optional" criteria for LDL-C level, 37.1% of the population, or at least 10 million Thais, would be eligible for treatment. This proportion would be greater in urban compared with rural areas within each age group and overall (46% vs 33%; p < 0.001), although the absolute number of Thai

Clinical Risk	LDL- C threshold for optional drug treatment**	LDL-C threshold for recommended drug treatment
< 2 CHD risk factors* \geq 2 CHD risk factors* and 10-year CHD risk < 10%	160-189 mg/dL (4.13-4.89 mmol/L) -	$\geq 190 \text{ mg/dL} (\geq 4.90 \text{ mmol/L})$ $\geq 160 \text{ mg/dL} (\geq 4.13 \text{ mmol/L})$
\geq 2 CHD risk factors* and 10-year CHD risk > 10-20%	-	\geq 130 mg/dL (\geq 3.36 mmol/L)
10-year CHD risk > 20% Diabetes (CHD equivalent)	100-129 mg/dL (2.58-3.35 mmol/L) 100-129 mg/dL (2.58-3.35 mmol/L)	\geq 130 mg/dL (\geq 3.36 mmol/L) \geq 130 mg/dL (\geq 3.36 mmol/L)

* CHD (coronary heart disease) risk factors include age (\geq 45 years in men; \geq 55 years in women); family history of premature CHD (male first degree relative < 55 years, female first degree relative < 65 years - in InterASIA first degree relative of either sex < 50 years of age was recorded); current cigarette smoking; hypertension or antihypertensive therapy; and HDL-cholesterol < 40 mg/dL (1.03 mmol/L). A HDL-cholesterol level 60 mg/dL (1.55 mmol/L) is a negative risk factor

10-year risk of fatal or nonfatal myocardial infarction, based on modified Framingham risk scoring sheets - separate functions in men and women using age, total cholesterol, current smoking status, and systolic blood pressure ** recommended target if lifestyle interventions fail - used for 'liberal scenario'

Age(y)			Rural					Urban		
))	Total cholesterol (mmol/l)	LDL cholesterol (mmol/L)	HDL cholesterol (mmol/L)	Total / HDL cholesterol ratio	Triglycerides (mmol/l)	Total cholesterol (mmol/l)	LDL cholesterol (mmol/L)	HDL cholesterol (mmol/L)	Total / HDL cholesterol ratio	Triglycerides (mmol/l)
Male	4.80 (0.08)	2.86 (0.08)	<i>I.06</i> (0.02)	4.74 (0.06)	2.15 (0.07)	5.54 (0.11)	3.61 (0.11)	1.19 (0.02)	4.89 (0.09)	<i>I.88 (0.06)</i>
35-44	4.70 (0.13)	2.74 (0.12)	1.05(0.05)	4.66(0.11)	2.14(0.08)	5.50(0.19)	3.57 (0.22)	1.20 (0.04)	4.83(0.19)	1.94(0.08)
45-54	4.79 (0.14)	2.83 (0.16)	1.05(0.04)	4.74 (0.06)	2.40(0.18)	5.60 (0.21)	3.68 (0.21)	1.15(0.03)	5.07 (0.06)	2.09(0.14)
55-64	4.91(0.11)	2.93 (0.12)	1.09(0.05)	4.77 (0.13)	2.03(0.18)	5.58(0.18)	3.60 (0.17)	1.23 (0.04)	4.89(0.19)	1.69(0.07)
≥65	(0.09)	3.12 (0.13)	1.07(0.03)	4.93 (0.09)	1.86(0.14)	5.50 (0.12)	3.62 (0.15)	1.22 (0.02)	4.73(0.10)	1.46(0.07)
Female	5.18(0.07)	3.28 (0.08)	1.13 (0.02)	4.77 (0.08)	1.73 (0.08)	5.71 (0.08)	3.71 (0.07)	I.34~(0.02)	4.49(0.10)	I.5I(0.07)
35-44	(0.09)	3.13 (0.12)	1.16(0.04)	4.45 (0.09)	1.51 (0.12)	5.41 (0.06)	3.47 (0.07)	1.37 (0.03)	4.11 (0.07)	1.27(0.08)
45-54	5.10(0.11)	3.18 (0.12)	1.13(0.03)	4.70 (0.04)	1.80(0.14)	5.77 (0.13)	3.73 (0.11)	1.34 (0.03)	4.60 (0.20)	1.63(0.15)
55-64	5.58 (0.12)	3.65 (0.14)	1.11(0.04)	5.25 (0.23)	1.97(0.17)	6.09(0.13)	4.06 (0.12)	1.31 (0.04)	4.88(0.05)	1.69(0.07)
<u>≥</u> 65	5.31 (0.18)	3.42 (0.19)	1.07(0.03)	5.15 (0.12)	1.92(0.13)	6.02(0.18)	3.97 (0.15)	1.28 (0.05)	4.95(0.05)	1.75(0.08)

Table 3.	Estimated mean levels and prevalence of other cardiovascular risk factors in the rural and urban Thai
	population, aged 35 years and older

Risk Factor	Rural	Urban	p value
Age (years)	50.8 (1.4)	50.2 (1.5)	0.23
Women (%)	51.3 (6.6)	53.1 (7.8)	0.88
SBP (mmHg)	119.0 (1.0)	122.0 (1.2)	0.06
DBP (mmHg)	75.0 (0.5)	78.0 (0.8)	<0.00
Current smoking (%)	26.8 (4.4)	20.8 (3.1)	10.32
Current alcohol consumption (%)	35.6 (3.7)	33.9 (3.2)	0.76
Diabetes (%)	8.5 (0.8)	11.9 (1.0)	0.02
Weight (kg)	58.3 (0.6)	62.0 (0.8)	0.001
Body mass index (kg/m ²)	23.6 (0.2)	24.7 (0.2)	<0.001
Waist circumference (cm)	79.5 (0.7)	83.6 (0.7)	<0.001
Waist-hip ratio	0.87 (0.006)	0.88 (0.008)	0.20
Mean (SE) or percent (SE), Weighted using SBP, systolic blood pressure; DBP, diastolic	sampling factors from the 200 blood pressure	0 Thai National Census popul	ation

Table 2. Estimated mean levels of plasma total cholesterol, HDL cholesterol, total / HDL cholesterol ratio and triglycerides in the rural and urban Thai . -1.1.2 . 1



Fig. 1 Prevalence (A) and absolute numbers (B) of Thai adults aged \geq 35 years eligible for lipid lowering drug treatment according to NCEP III guidelines, stratified by age and rural or urban residence. The data shown reflect liberal estimates where "drug optional" individuals would also be treated

adults eligible for aggressive lipid reduction would be greatest in rural areas (6.2 vs 3.9 million). Under the more conservative "drug recommended" criteria for LDL-C, 22% of the population (27% urban vs 20% rural; p = 0.01) would qualify for treatment.

Table 4 shows the distribution of adults in rural and urban areas, when stratified by the threshold values of HDL-C and LDL-C used in the NCEP-ATP III guidelines. A greater proportion of urban than rural residents had a LDL-C level \geq 130mg/dL or 3.36 mmol/L (59 vs 36%; p < 0.001). Compared with rural areas, the proportion of individuals with HDL-C level < 40 mg/dL (1.03 mmol/L) in urban areas was lower (24 vs 44%; p <0.001), while for the proportion with HDL-C level \geq 60 mg/dL (1.55 mmol/L), the opposite was true (18 vs 7%; p = < 0.001).

Table 4. Proportion (SE) of rural and urban Thais aged \geq 35 years with LDL-cholesterol and HDL-cholesterol levels stratified according to NCEP III threshold

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Discussion

The present study provides the most comprehensive and reliable estimates of the population distribution of serum lipid parameters in the adult Thai population to date. In 1991, a population-based survey of the Thais aged \geq 30 years estimated mean total cholesterol values of 4.8 mmol/L for men and 5.1 mmol/L for women⁽¹¹⁾. The current mean levels of 5.03 mmol/L in men and 5.35 mmol/L in women suggest that cholesterol levels among Thai adults have risen. These findings are consistent with the substantial increases in cholesterol observed between 1985 and 1997 in an urban occupational cohort in Thailand⁽¹²⁾. At a population level, even small changes in serum cholesterol level are likely to have important implications for the incidence of atherothrombotic disease. In a recent meta-analysis of cohort studies conducted in the Asia-Pacific region, each 1 mmol/L higher level of usual total cholesterol was associated with a 45% (95% CI 35-55%) greater relative risk of nonfatal myocardial infarction or coronary death⁽¹³⁾. These findings have particular relevance for urban-dwelling Thais, who have substantially higher values of TC and LDL-C. The current rural-urban difference in mean TC values of about 0.7 mmol/L would translate into a 25-35% higher risk of coronary heart disease in urban populations based on this risk factor alone.

The higher mean HDL-C values in urban compared to rural regions was unexpected, and resulted in a lipid profile among urban populations that on the basis of TC/HDL-C ratio was no more adverse than the lipid profile of rural populations. Another unanticipated observation was that of higher mean TG levels among the rural compared with the urban populations. These findings for lipids are discordant with the observed higher levels in urban populations of other "metabolic abnormalities" associated with cardiovascular disease, such as waist circumference, blood pressure and diabetes. This pattern of rural-urban difference in serum lipid profiles has been described previously in both Thai⁽¹⁴⁻¹⁷⁾ and other developing country populations^(18,19). However, in most studies, from both developing and developed regions of the world and including the Chinese component of InterASIA(20), rural inhabitants are shown to have lower TC, higher or similar HDL-C (and thus lower TC / HDL-C ratio) and lower TG levels, compared with their urban counterparts⁽²¹⁻²⁶⁾. A possible explanation for the lipid profile observed amongst the rural Thai population in the current study relates to diet. Other data suggest that the percentage of total dietary energy intake comprised of carbohydrates is exceptionally high in certain populations of rural Thailand, up to 80% in one study^(14,27). In terms of atherosclerotic risk, the significance of the lipid profile associated with a sustained low-fat high-carbohydrate diet is unclear and remains an issue of considerable controversy⁽²⁸⁻³⁰⁾.

If the US-based NCEP-ATP III lipid lowering treatment guidelines were followed, about one-third of the adult Thai population aged \geq 35 years would qualify for lipid lowering drug therapy for the primary prevention of coronary heart disease. The NCEP-ATP III guidelines currently identify a higher proportion of Thai than US adults for drug treatment. Using the Third Annual National Health and Nutrition Survey (NHANES III -1988 to 1994), 25% of the US population aged ≥ 20 years would be eligible for treatment under NCEP-ATP III guidelines⁽³¹⁾. Among those aged ≥ 65 years, this would correspond to 39% of the US population, compared with 48% of the Thai population. These findings have major economic and resource implications for Thailand, but also raise a more fundamental question about the generalisability of the NCEP-ATP III guidelines to populations other than that from which it was derived. A probable explanation for the high proportion of Thais identified relates to the use of the Framingham risk function in NCEP-ATP III⁽⁷⁾. Without recalibration of the algorithm using local disease incidence rates and risk factor prevalence data, the 10-year absolute risk of coronary heart disease is likely to be systematically over-estimated in the Thai population^(32,33). In addition, the NCEP-ATP III guidelines consider a HDL-C level of < 40 mg/dL (1.03 mmol/L) as a positive risk factor, and a HDL-C level of $\geq 60 \text{ mg/dL}$ (1.55 mmol/L) as a negative risk factor towards determining eligibility for lipid-lowering treatment. Among the adult Thai population aged \geq 35 years, a substantially higher proportion of rural than urban residents have low HDL-C based on these criteria, while the reverse is true for high HDL-C. This raises the possibility of the inappropriate identification of some individuals for treatment on the basis of HDL levels using these cut-points in Thailand.

One potential limitation of the presented analyses relates to the calculation of LDL-C using Friedewald's equation after an overnight fast of 8 hours. Although this fasting period has been defined by some as the minimum required for LDL-C calculation, a 12 hour fast is generally considered ideal (as was the procedure in NHANES-III)^(34,35). The shorter fasting period may have resulted in under-estimation of LDL-C levels in InterASIA; however, this suggests that an even higher proportion of adult Thais may be eligible for lipid-lowering therapy using NCEP-ATP III guidelines than the presented data indicate.

With increang urbanisation of the population, the findings of the present study have important implications for the future burden of atherosclerotic diseases in Thailand, and underscore the urgent need to develop and implement cost-effective preventive strategies. Without detracting from the importance of reliably identifying high-risk individuals who would benefit the most from cardiovascular risk reduction therapy, the current NCEP-ATP III recommendations for lipid lowering therapy are unlikely to be directly applicable to the Thai population. This does not necessarily imply the need to establish new Thai-specific cohort data, which would be costly and take years to yield useful information. Numerous studies have shown that existing risk functions (e.g. Framingham) can be effectively "recalibrated" for different populations, using reliable national data on risk factor prevalence and disease incidence^(32,36). Such countryspecific approaches to risk prediction and subsequent treatment protocols are essential to obtain maximum benefit from future health resource allocation in countries such as Thailand.

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ภาวะไขมันผิดปกติในคนไทยชนบทและในเมือง

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ใด้ทำการตรวจเลือดคนไทยในชนบทและในเมืองตั้งแต่อายุ 35 ปี ขึ้นไป จำนวน 5,305 ราย พบว่า

- โคเลสเตอรอลในชายชนบท : เมืองเป็น 4.8:5.54 mmol/L
 โคเลสเตอรอลในหญิงชนบท : เมืองเป็น 5.18:5.71 mmol/L
 ค่า p < 0.001 ทั้งในชายและหญิง
- HDL ในชายในชนบท : เมืองเป็น 1.06:1.19 mmol/L
 HDL ในชายในชนบท : เมืองเป็น 1.13:1.34 mmol/L
 ค่า p < 0.001 ทั้งชายและหญิง
- LDL ในชายในชนบท : เมืองเป็น 2.15:1.88 mmol/L
 LDL ในชายในชนบท : เมืองเป็น 1.73:1.51 mmol/L
 ค่า p = 0.01 ทั้งชายและหญิง

ทาย – 0.01 พรษายและหญง การศึกษานี้พบว่าประชากรร้อยละ 37 หรือ 10 ล้านคน มีความรู้และใช้ยาเพื่อลดไขมันในร่างกาย ซึ่งไม่น่าเชื่อว่ากลุ่มคนจะมากขนาดนี้ที่มีไขมันสูง ดังนั้นควรมีมาตรการเพื่อหยุดยั้งการมีไขมันสูงโดยด่วน และพัฒนา กฎหมายเพื่อใช้ควบคู่ไปกับการรักษาปัจจัยเสี่ยงต่าง ๆ ที่เข้ากันได้กับพื้นเพของชีวิตคนไทย