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Predictors in Youth of Adult Cardiovascular Events

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Data availability can be requested from the i3c Steering Committee.

Author Contributions:

Nuotio had full access to the data in the study and takes responsibility for the ingerity of the data and the accuracy of the data analysis.

Nuotio and Laitinen substantially contributed to the conception and the design of the study, researched the data, wrote the manuscript, and reviewed the manuscript critically for important intellectual content.

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design, acquired data, contributed to discussion, and reviewed the manuscript critically for important intellectual content.

Kartiosuo and Koskinen substantially contributed to the conception and the study design, contributed to discussion, and reviewed the manuscript critically for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

BMI=body mass index

CVD =cardiovascular disease

i3C=International Childhood Cardiovascular Cohort

ICD=International Classification of Diseases

NHLBI=National Heart, Lung, and Blood Institute

ABSTRACT

BACKGROUND AND OBJECTIVES: Childhood risk factors are associated with cardiovascular events in adulthood. However, further information is needed on clinical-setting risk assessment. We compared the utility of a risk model based solely on nonlaboratory risk factors in adolescence versus a model additionally including lipids to predict cardiovascular events in adulthood.
METHODS: The study comprised 11,550 participants from seven longitudinal cohort studies in the United States, Australia, and Finland, with risk factor measurements at 12-19 years of age who were followed into adulthood. The adolescent risk factors were defined using current clinical standards and were overweight/obesity, elevated blood pressure, smoking, and borderline high/high levels of total cholesterol and triglycerides. Main outcomes were medically adjudicated fatal or nonfatal cardiovascular disease events occurring after age 25.
RESULTS: Of 11,550 participants (55.1% female, mean age 50.0±7.7 years), 513 (4.4%) had confirmed cardiovascular events. In multivariable model (Hazard Ratio [95% confidence interval]), elevated blood pressure (1.25[1.03–1.52]), overweight (1.76[1.42–2.18]), obesity (2.19[1.62–2.98]), smoking (1.63[1.37–1.95]), and high total cholesterol (1.79[1.39–2.31]) were significant predictors of cardiovascular events ($P<0.05$). Addition of lipids (total cholesterol and triglycerides) into the nonlaboratory model (age, sex, blood pressure, body mass index and smoking) did not improve discrimination in predicting cardiovascular events (C statistics for lipid model 0.75[SD 0.07] and for nonlaboratory model 0.75[0.07], $P=0.82$).
CONCLUSION: Nonlaboratory-based risk factors and lipids measured in adolescence independently predicted adult cardiovascular events. The addition of lipid measurements to nonlaboratory risk factors did not improve prediction of cardiovascular events.

Word count: 246 words

KEY WORDS: adolescence, adult, cardiovascular risk factors, cardiovascular disease, cohort study.

Article Summary:

This study examines whether prediction of future cardiovascular events in youth could be alternatively performed without laboratory tests using longitudinal data from seven cohorts.

What's Known on This Subject:

Cardiovascular disease is a multifactorial disease with its roots in childhood and primordial prevention would ideally be targeted to children and adolescents with modifiable risk factors. Lipid screening in adolescence could allow early identification of dyslipidemia but requires substantial resources.

What This Study Adds:

An approach that used only nonlaboratory risk factors obtained in youth predicted cardiovascular events as accurately as one additionally containing information on lipids. This nonlaboratory approach offers a simple alternative to identify adolescents at risk when laboratory testing is inconvenient.

INTRODUCTION

Atherosclerosis is a multifactorial disease with its roots in childhood. (1,2) Recently, we showed that childhood cardiovascular risk factors of body-mass index, systolic blood pressure, total cholesterol level, triglyceride level, and youth smoking, particularly in combination beginning in early childhood, were associated with adult cardiovascular events and death from cardiovascular causes before the age of 60 years. (3) These data suggest that primordial prevention of cardiovascular disease (CVD) should be targeted to children and adolescents.

In 2011, the National Heart, Lung, and Blood Institute recommended universal screening of lipid levels in youth (4). By contrast, in 2023, the US Preventive Services Task Force did not recommend screening in general risk assessment, arguing that the evidence to demonstrate its effectiveness was insufficient.(5) In addition, the 2018 multi-society lipid guideline and the ESC/EAS lipid guideline recommended lipid screening for children and adolescents with family history of either early CVD or significant hypercholesterolemia. (6,7) Further, the International Atherosclerosis Society guidance for familial hypercholesterolemia recently provided recommendations regarding lipid measurements suggesting that multiple screening strategies (selective, opportunistic and/or universal) should ideally be used to detect familial hypercholesterolemia. (8) There thus exists inconsistency in the messages that pediatric care providers are receiving from expert bodies.

Efforts to create a risk stratification system that could simplify general risk assessment in situations where laboratory testing is inconvenient or unavailable are needed. A study in adults (9) showed promising results supporting this kind of approach, with a nonlaboratory-based risk model predicting CVD events as accurately as one that relied on laboratory-based measurements. We previously reported that addition of lipid measurements to traditional clinic-based risk factor assessment provided a statistically significant but clinically modest improvement on adolescent prediction of high carotid intima-media thickness in adulthood. (10)

In this study, we use data from the International Childhood Cardiovascular Cohort (i3C) Consortium that includes seven longitudinal cohort studies (Australia, Finland, and five in the United States) of cardiovascular risk factors initiated in childhood that have followed participants into adulthood. Our aim was to compare risk prediction models based on nonlaboratory versus nonlaboratory plus lipid data obtained at ages 12-19 years for predicting adult CVD events. The analyses of this study relate to the aspect of general pediatric lipid screening and do not address the purpose related to familial hypercholesterolemia.

2. METHODS

2.1. Study Sample

The sample comprised 11,550 participants aged 12-19 years at baseline from the International Childhood Cardiovascular Cohort (i3C) Consortium, in seven childhood cohorts from the United States, Australia, and Finland. (11,12) Data from the first available study visit was used within the age range of 12-19 years of age. All risk factor measurements were derived from the same study visit. All seven cohorts included in this analysis have been previously described in detail (11), and a brief description of the cohorts is provided in the online supplement. The cohort studies followed protocols approved by local ethics committees, with signed informed consent or assent for participants as children or adolescents. All cohorts had data collected in clinical examinations that obtained the participants' age, sex, height and weight, and blood pressure. Fasting levels of plasma or serum lipid and lipoprotein measurements were measured by standard methods. Data on youth smoking was based on reports by the participants during childhood augmented by adult recall of the smoking initiation date and was analyzed as a dichotomous variable (yes vs. no). (3)

Between 2015-2019 the i3C Consortium conducted a coordinated study to locate and survey the now-adult participants. (3) US and Australian participants completed a Heart Health Survey to self-report cardiovascular events and medical procedures and update other relevant information; National Death

Indices were also searched to determine cause of death of participants. Cardiovascular event data for the Finnish participants through December 31, 2018 were obtained from Finland's national medical registries. Altogether, 20,659 participants were personally located or identified as deceased with a coded cause of death. Of these 20,659, this report includes 11,550 participants who had data available between 12-19 years of age, the age range when smoking data were collected.

2.2. Definition of Risk Factors During Adolescence

To increase generalizability of these data to the clinical setting and to be consistent with current recommendations, we analyzed the data by using categorical adolescent risk factors. Overweight status was defined according to the extended international (International Obesity Task Force; IOTF) cut-offs for body mass index (BMI).(13) Elevated blood pressure was defined according to the Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents.(14) High-risk plasma lipid levels were defined according to the National Heart, Lung, and Blood Institute guidelines.(4)

2.3. Cardiovascular events

The primary study endpoint was the first instance of fatal or non-fatal myocardial infarction, stroke, transient ischemic attack, ischemic heart failure, angina, peripheral artery disease, carotid intervention, abdominal aortic aneurysm, or coronary revascularization recorded in physician or hospital records or identified through coded cause of death. Non-fatal events were self-reported in the Heart Health Survey by US and Australian participants, and medical records were requested for confirmation. A physician adjudication committee reviewed the records and classified each event as confirmed cardiovascular disease, not an event, or not adjudicable. Fatal event diagnoses were adjudicated using ICD coded causes of death. In Finland, diagnoses of fatal and non- fatal CVD events were based on ICD codes obtained from the national medical or death registries.

2.4. Statistical Methods

Statistical analyses were performed with SAS 9.4. Statistical significance was inferred at a 2-tailed value of $P \leq 0.05$. The normality assumptions of the residuals were assessed by examining histograms of the residuals and normal probability plots. To examine the associations of exposures in adolescence and subsequent cardiovascular events, analyses of survival data based on the Cox proportional hazards model were used. All analyses were adjusted for age, sex and study cohort. The ability of nonlaboratory model (including age, sex, study cohort, blood pressure, BMI, smoking) and lipid model (nonlaboratory model and additionally total cholesterol and triglycerides) data in adolescence to predict CVD events in adulthood was assessed using Uno's C-statistics in all study participants and in various subgroups. (15) Additionally, a more straightforward yet naïve Harrell's C-statistics were calculated for similar models to further assess the predictive abilities. While the Harrel's C statistic calculates the percentage of only comparable pairs whose risk has been correctly identified by the model and discards the pairs that are incomparable due to censoring, Uno's method is independent of the censoring. The differences between the AUC functions were calculated using Uno's inverse probability of censoring weighting technique. The confidence limits were calculated based on perturbation resampling. (16) We also calculated category-free net reclassification improvement (NRI) and integrated discrimination improvement (IDI) to examine whether based on these statistics the addition of lipids enhances prediction of CVD events compared to nonlaboratory model. (17) Models were tested for multicollinearity using the variance inflation statistic and no sign of multicollinearity was observed (variance inflation statistic <2.0 for all variables).

RESULTS

Characteristics of the study participants

Risk factors of the study participants at ages 12-19 years are described in Table 1. Of 11,550 participants (55.1% female, mean age 50.0 ± 7.7 years when outcome data were obtained during adulthood), 513 (4.4%) had confirmed cardiovascular events**.** Characteristics of study participants and those not included in the analyses due to insufficient data are compared in the Supplemental Table 1.

Nonlaboratory- Versus Lipid- (i.e., Nonlaboratory with Lipid Measurements) Based Risk Assessment in Predicting CVD events in Adulthood

Univariable analyses (Table 2) assessing relations between risk factors and CVD events showed significant associations for age, sex, and most of categorical risk factors (overweight, obesity, elevated blood pressure, smoking, high total cholesterol, high triglycerides, borderline low HDL cholesterol, low HDL cholesterol, and high LDL cholesterol). Table 3 shows the results for a multivariable model assessing risk ratios for CVD events in adulthood according to nonlaboratory and lipid risk factors measured during adolescence. Among the nonlaboratory risk factors, overweight, obesity, elevated blood pressure, and smoking remained significantly associated with CVD events. When lipids (total cholesterol and triglycerides) were introduced into the model, the significant associations for overweight, obesity, elevated blood pressure, and smoking remained, with high total cholesterol also significant. When total cholesterol was replaced with LDL-cholesterol and HDL-cholesterol in the lipid model (lipid model including LDL-cholesterol, HDL-cholesterol, and triglycerides; N=8,048), the significant association remained for overweight, obesity, elevated blood pressure, smoking, and high LDL-cholesterol. (Supplemental Table 2).

As shown in Figure 1, both in nonlaboratory and lipid (nonlaboratory plus lipids) models the number of adolescence risk factors was associated with subsequent cardiovascular events.

Figure 2 shows the receiver operating characteristic curve values (Uno's C-statistics) for the nonlaboratory (blood pressure, BMI, smoking) and lipid model (nonlaboratory plus total cholesterol and triglycerides) prediction of adult CVD events. The addition of lipids to the nonlaboratory model did not lead to higher C statistics (C statistics for lipid model 0.75 [SD 0.07] and for nonlaboratory model 0.75 [0.07], P=0.82). When males and females, smokers and non-smokers, participants with normal weight and overweight, participants within US-cohorts, and participants within non-US-cohorts were analyzed separately, the results remained essentially similar (Figure 2). When Harrell's C-statistics, were calculated for similar models (Supplemental Table 3), the results were essentially similar to those shown in Figure 2. The overall improvement in category-free NRI was 0.11 (95% CI 0.008-0.21); for cases it was -0.03 and for controls 0.14, indicating that the addition of lipids improves the prediction of non-events rather than events. However, IDI was 0.002 (P-value 0.89) indicating that the difference in average predicted risks between the individuals with and without the outcome did not increase significantly when lipids were included in the prediction model.

When only fatal CVD events were used as an outcome, the results remained essentially similar. The number of adolescence risk factors was associated with fatal CVD events in both nonlaboratory and lipid models (Supplemental Figure 1). In C-statistics, no significant difference was observed when lipids were added to the nonlaboratory model (C statistics for lipid model 0.75 [SD 0.05] and for nonlaboratory model 0.72 [0.06], P=0.14).

DISCUSSION

The findings from seven international longitudinal cohorts examined in this study show that the risk of CVD events can be predicted by nonlaboratory adolescent risk factors (overweight, obesity, hypertension, and smoking). Lipid values were also associated with adult CVD events; however, addition of lipids did not improve models of prediction for CVD events.

In our recent report we showed that childhood cardiovascular risk factors, BMI, systolic blood pressure, smoking, total cholesterol, and triglycerides, were significantly associated with incident adult CVD events by midlife. (3) Previously, data from the Coronary Artery Risk Development in Young Adults study showed a relation between the Framingham risk score and cardiovascular events in a young adult cohort (age 22-36) followed for 20 years. (18) It is noteworthy to mention that the original Framingham risk score does not include BMI/obesity and when obesity is included the overall prediction does not change. (19) However, BMI in childhood and overweight/obesity in late adolescence have been associated with increased cardiovascular morbidity and mortality in adulthood. (20, 21) The findings of the present study are consistent with the earlier observations showing the relation of early risk factor profiling to CVD events.

In the National Health and Nutrition Examination Survey I adult population (baseline, 25–74 years of age, N=14,407), Gaziano et al. (9) examined whether a risk prediction model that did not require any laboratory tests could be as accurate as one requiring laboratory information. They observed that a model with nonlaboratory-based risk factors predicted CVD events as accurately as one that relied on laboratory-based values. The nonlaboratory model included age, blood pressure, smoking, BMI, history of diabetes mellitus, and history of blood pressure treatment, whereas in the laboratory-based model, BMI was replaced with total cholesterol level. In addition, the Fuster-BEWAT Score (blood pressure, exercise, weight, alimentation and tobacco) that requires no laboratory tests has been shown to predict the presence and extent of subclinical atherosclerosis in adults with similar accuracy than

the ideal cardiovascular health score that is recommended for use in primary prevention.(22) Accordingly, we previously reported that the addition of adolescent lipid measurements to traditional clinic-based risk factor assessment (sex, blood pressure status, body mass index status) provided a statistically significant but clinically modest improvement on prediction of high carotid intima-media thickness in adulthood (10). In the present study, our findings from seven cohort studies among youth 12 to 19 years of age were essentially similar. Even though, in line with our prior analyses (3), adolescent lipid levels in this substudy were related with CV events, nonlaboratory-based risk factors predicted CVD events as accurately as an approach that additionally considered lipids. Our results were consistent in several subgroup analyses based on sex, study cohort location, smoking and adiposity status. Furthermore, we did observe statistically significant improvement in the category-free NRI. However, there was no improvement in IDI in the prediction of CVD events when laboratory model was compared to nonlaboratory model. Thus, it is likely that such small movement noticed in the NRI is not clinically relevant. There are several possible explanations for this finding. First, within the baseline age range of our study cohort, there are substantial changes in the lipid profile related especially to pubertal development and growth. (23) These physiologic changes may reduce the ability of the lipid profile to add to the risk prediction. Second, the variables in the nonlaboratory model, especially BMI and blood pressure contain information about the lipid levels (24), so this model partly, implicitly, includes lipids. Third, especially compared to BMI measurements, there is more physiological (long term) and analytical variation (day-to-day) in lipid values and thus use of repeated lipid measures instead of a single measure could improve the predictive performance of lipids (25).

Strong evidence suggests that CVD has its origins in childhood. (1,2) Prevention strategies conducted in children have provided evidence of benefits of lifestyle counselling on risk markers and remain the cornerstones for promoting cardiovascular health in children at the population level (2). Recently, the STRIP study (Special Turku Coronary Risk Factor Intervention Project for Children) showed

favorable effects on risk factors over a period of 26 years after dietary counselling initiated in infancy and continued throughout childhood. (26) In addition to the population strategy, the identification of children who are at high risk of atherosclerosis could be effective in allowing personalized interventions. However, there is no widely accepted childhood or adolescent risk prediction method that uses risk factor data obtained from apparently healthy youths. From the Pathobiological Determinants of Atherosclerosis in Youth data, a risk score has been developed estimating the probability for coronary artery lesions observed at autopsy, but it is only applicable for individuals 15 to 34 years of age. (27,28)

Results from the present study suggest that a risk prediction method based on BMI, blood pressure and smoking status that does not require any laboratory tests could be non-inferior to one requiring laboratory information. This nonlaboratory approach would allow an easy and simple initial evaluation/identification of those youth who might benefit from a further investigation of major modifiable cardiovascular risk factors, such as lipids, and therapeutic lifestyle and possible medical interventions. Obvious benefits include avoiding the need to subject a child or adolescent to a blood draw, as well as reduced financial costs. Earlier (from 2011) pediatric guidelines recommend lipid screening for identifying familial hypercholesterolemia and predicting atherosclerosis (4). We acknowledge that our findings do not provide any evidence for or against screening for familial hypercholesterolemia, which is an important reason to measure lipid levels in childhood as a clearly defined risk factor for atherosclerotic CVD occurring in 1:250 individuals (29). Furthermore, lipid measures might enhance the discrimination of individuals already in the high-risk group as participants with all of 5 risk factors of lipid model had notably higher risk for subsequent cardiovascular event (HR 6.20; 95%CI 3.59-10.73) compared to participants with all three risk factors of nonlaboratory model (HR 4.05; 95%CI 2.92-5.64).

STUDY LIMITATIONS

Strengths of the study include the large sample size, longitudinal study design, extensive follow-up of the participants who were very well-phenotyped in adolescence among seven cohorts, and adjudication of medical records. However, it was not possible to locate half of the original adolescent participants, and medical records were not available for some participants self-reporting a cardiovascular event (included in the non-event group). Second, we were unable to consider family history for e.g. familial hypercholesterolemia or pubertal stage, both of which may have an influence on CVD risk factors, because data were not available for all cohorts. Third, lipid measurement methods differed between study cohorts. However, to take this into account, the analyses were adjusted for cohort. Finally, residual confounding is a possibility in all observational studies.

CONCLUSIONS

In summary, our data from seven international cohort studies show that both nonlaboratory risk factors and lipids in adolescence independently predict adult CVD events. The predictive value of an approach that additionally considered lipids using current clinical standards was not superior to a model that only included nonlaboratory factors.

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FIGURE LEGEND

Figure 1. Hazard ratios for cardiovascular disease event according to the number of risk factors stratified by nonlaboratory and lipid (nonlaboratory plus lipids) models.

If a risk factor was above normal cut points derived from the recommendations of the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents or participant reported smoking, the risk factor was considered positive.

Figure 2. Receiver operating characteristic (ROC) curve values for a model only including age and sex and comparisons of nonlaboratory (age, sex, blood pressure, BMI, smoking) with lipid model (additionally total cholesterol and triglycerides) in adolescents for prediction of adult cardiovascular events.

Table 1. Participant characteristics

	BHS		CDAH		MN		Muscatine*		NGHS		Princeton		YFS		All	
N	2,862		426		362		4,259		436		423		2,782		11,550	
Sex (% female)	56.9		51.4		45.6		52.5		100.0		54.6		52.0		55.1	
Age at baseline, y	13.9	1.5	14.0	1.5	14.5	1.9	14.0	1.6	16.9	2.7	15.1	1.9	14.2	2.4	14.2	2.0
Age at censoring, y	47.2	7.2	46.2	2.2	32.4	2.5	54.9	5.7	40.2	1.3	56.6	5.7	48.8	5.1	50.0	7.7
Total cholesterol, mmol/L	4.16	0.74	4.45	0.75	3.88	0.72	4.02	0.70	4.21	0.83	4.40	0.83	5.14	0.92	4.36	0.90
LDL-C, mmol/L	2.37	0.66	2.68	0.69	2.27	0.62	2.25	0.60	2.53	0.75	2.75	0.76	3.21	0.84	2.69	0.83
HDL-C, mmol/L	1.52	0.49	1.42	0.30	1.13	0.26	1.27	0.26	1.34	0.28	1.33	0.32	1.57	0.32	1.47	0.40
Triglycerides, mmol/L	0.84	0.44	0.75	0.37	1.05	0.61	0.89	0.43	0.98	0.50	0.91	0.42	0.79	0.36	0.86	0.43
BMI, kg/m^2	20.9	4.6	19.5	2.8	23.0	5.5	20.8	3.7	24.2	6.8	21.4	4.5	19.3	3.0	20.6	4.2
Systolic blood pressure, mmHg	107	9	113	13	108	9	115	13	108	9	109	12	115	11	112	12
Diastolic blood pressure, mmHg	54	12	67	12	57	13	66	12	67	9	67	10	67	10	63	13
Smoking (%)	42.8		34.5		34.0		34.7		39.7		35.9		42.6		38.8	
CVD events (%)**	139 (4.9)		4 (0.9)		0 (0)		252 (5.9)		3 (0.7)		31 (7.3)		84 (3.0)		513 (4.4)	

BMI= body mass index, HDL-C = High-density lipoprotein cholesterol, LDL-C = Low-density lipoprotein cholesterol, CVD = Cardiovascular disease

Values are mean (SD) unless otherwise stated.

*LDL-C and HDL-C only available in subsample of 812 participants in the Muscatine Study

**213 (35%) of the events were fatal

Table 2. Hazard Ratios for cardiovascular disease events in adulthood according to nonlaboratory risk factors and lipids.

Adolescent Risk Factor	Number of participants with event / total number	HR	95% CI
Age, y	513/11,550	1.10	1.05-1.16
Sex, male	513/11,550	2.12	1.77-2.54
Blood pressure*			
Normotensive	267/7,383	Ref	
Elevated blood pressure	246/4,167	1.45	1.20-1.75
Body mass index**			
Normal weight	314/9,098	Ref	
Overweight	118/ 1,754	1.96	1.59-2.42
Obese	54/ 698	2.73	2.04-3.65
Smoking			
Non-smoker	237/7,070	Ref	
Smoker	276 /4,480	1.67	1.40-1.99
Total cholesterol			
Normal (<4.40 mmol/L)	287/6,660	Ref.	
Borderline high (≥4.40-5.17)	122/2,940	1.17	0.95-1.46
High (≥5.18)	104/1,950	2.03	1.58-2.61
Triglycerides			
Normal (<1.02 mmol/L)	339/8,599	Ref	
Borderline high (≥1.02–1.46 mmol/L)	107/2,072	1.19	0.95-1.48
High (≥1.46 mmol/L)	67/879	1.82	1.39-2.37
LDL cholesterol			
Normal (<2.85 mmol/L)	169/5,093	Ref.	
Borderline high (≥2.85–3.36 mmol/L)	43/1,456	1.16	0.82-1.66
High (≥3.37 mmol/L)	68/1,511	1.93	1.39-2.68
HDL cholesterol			
Normal (>1.16 mmol/L)	205/6,419	Ref.	
Borderline low (1.16-1.03 mmol/L)	32/785	1.53	1.05-2.24
Low (<1.03 mmol/L)	42/872	1.74	1.23-2.44

*Age- and sex-specific values defined according to the Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents.
**Age- and sex-specific values defined according to the Cole classification.
Analyses adjusted additionally for age in adolescence, sex and study cohort.

Table 3. Multivariable Hazard Ratios for cardiovascular disease event according to a nonlaboratory model and a lipid model including additionally total cholesterol and triglycerides.

		Nonlaboratory model		**Lipid Model**	
Number of participants with event / total number		513/11,550		513/11,550	
Adolescent Risk Factor		HR	95 %CI	HR	95 %CI
Blood pressure*	Normotensive	Ref.		Ref.	
	Elevated blood pressure	1.27	1.04-1.54	1.25	1.03-1.52
Body mass index**	Normal weight	Ref.		Ref.	
	Overweight	1.83	1.48-2.27	1.76	1.42-2.18
	Obese	2.48	1.84-3.33	2.19	1.62-2.98
Smoking	Non-smoker	Ref.		Ref.	
	Smoker	1.63	1.37-1.94	1.63	1.37-1.95
Total Cholesterol	Normal (<4.40 mmol/L)			Ref.	
	Borderline high (≥4.40-5.17)		N/A	1.10	0.88-1.37
	High (≥5.18)			1.79	1.39-2.31
Triglycerides	Normal (<1.02 mmol/L)			Ref.	
	Borderline high (≥1.02–1.46 mmol/L)		N/A	1.03	0.82-1.28
	High (≥1.46 mmol/L)			1.27	0.96-1.69

*Age- and sex-specific values defined according to Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents.

**Age- and sex-specific values defined according to the Cole classification.

Analyses adjusted additionally for age in adolescence, sex, and study cohort.

Figure 1.

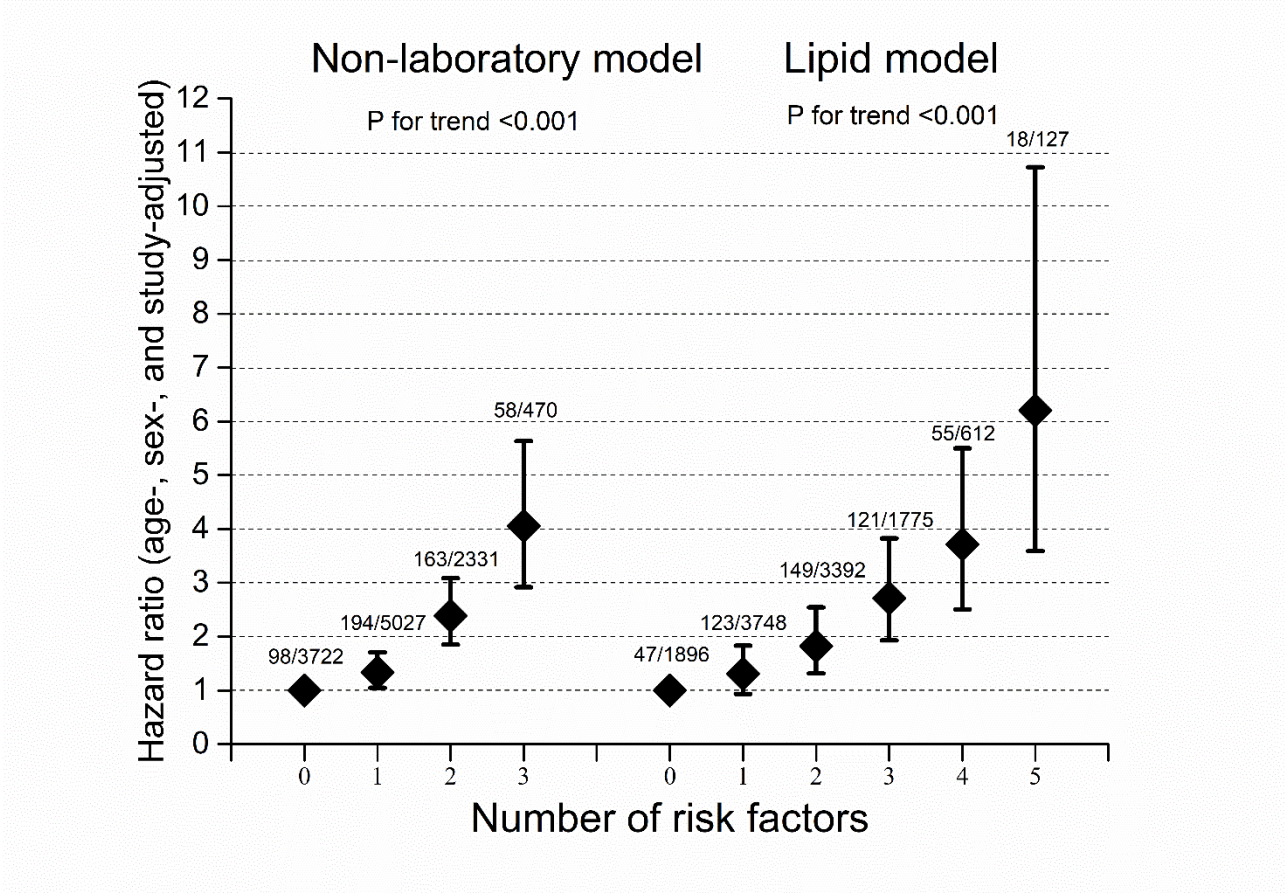
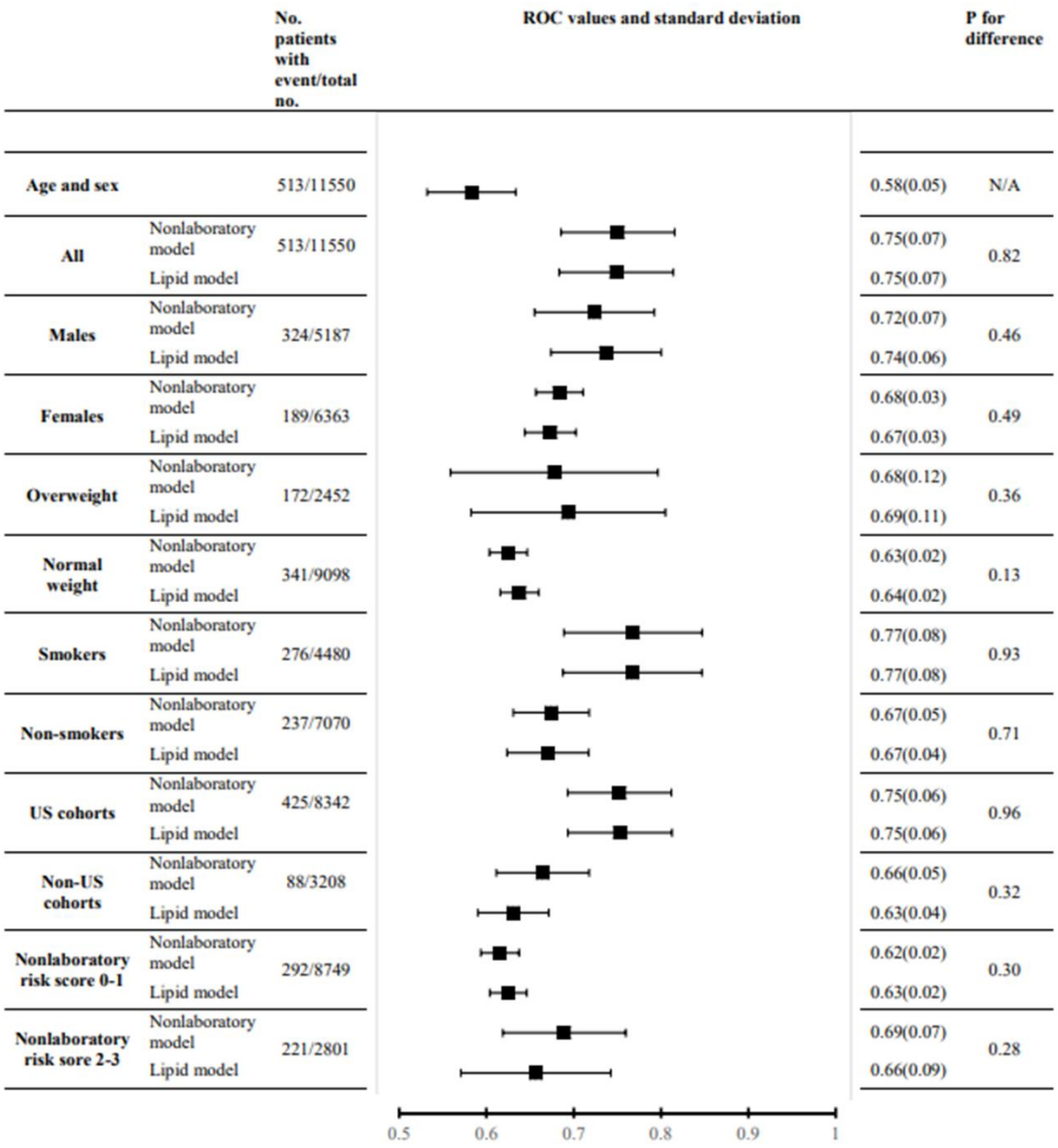

Non-laboratory model
Lipid model
P for trend <0.001
P for trend <0.001
Hazard ratio (age-, sex-, and study-adjusted)
Number of risk factors
98/3722
194/5027
163/2331
58/470
47/1896
123/3748
149/3392
121/1775
55/612
18/127

Figure 2.


No. patients with event/total no.
ROC values and standard deviation
P for difference
Age and sex
513/11550
0.58(0.05)
N/A
All
Nonlaboratory model
Lipid model
513/11550
0.75(0.07)
0.75(0.07)
0.82
Males
Nonlaboratory model
Lipid model
324/5187
0.72(0.07)
0.74(0.06)
0.46
Females
Nonlaboratory model
Lipid model
189/6363
0.68(0.03)
0.67(0.03)
0.49
Overweight
Nonlaboratory model
Lipid model
172/2452
0.68(0.12)
0.69(0.11)
0.36
Normal weight
Nonlaboratory model
Lipid model
341/9098
0.63(0.02)
0.64(0.02)
0.13
Smokers
Nonlaboratory model
Lipid model
276/4480
0.77(0.08)
0.77(0.08)
0.93
Non-smokers
Nonlaboratory model
Lipid model
237/7070
0.67(0.05)
0.67(0.04)
0.71
US cohorts
Nonlaboratory model
Lipid model
425/8342
0.75(0.06)
0.75(0.06)
0.96
Non-US cohorts
Nonlaboratory model
Lipid model
88/3208
0.66(0.05)
0.63(0.04)
0.32
Nonlaboratory risk score 0-1
Nonlaboratory model
Lipid model
292/8749
0.62(0.02)
0.63(0.02)
0.30
Nonlaboratory risk sore 2-3
Nonlaboratory model
Lipid model
221/2801
0.69(0.07)
0.66(0.09)
0.28
0.5
0.6
0.7
0.8
0.9
1