Clustering of cardiovascular risk factors and carotid intima-media thickness: The USE-IMT study

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Abstract

Background

The relation of a single risk factor with atherosclerosis is established. Clinically we know of risk factor clustering within individuals. Yet, studies into the magnitude of the relation of risk factor clusters with atherosclerosis are limited. Here, we assessed that relation.

Methods

Individual participant data from 14 cohorts, involving 59,025 individuals were used in this cross-sectional analysis. We made 15 clusters of four risk factors (current smoking, overweight, elevated blood pressure, elevated total cholesterol). Multilevel age and sex adjusted linear regression models were applied to estimate mean differences in common carotid intima-media thickness (CIMT) between clusters using those without any of the four risk factors as reference group.

Results

Compared to the reference, those with 1, 2, 3 or 4 risk factors had a significantly higher common CIMT: mean difference of 0.026 mm, 0.052 mm, 0.074 mm and 0.114 mm, respectively. These findings were the same in men and in women, and across ethnic groups. Within each risk factor cluster (1, 2, 3 risk factors), groups with elevated blood pressure had the largest CIMT and those with elevated cholesterol the lowest CIMT, a pattern similar for men and women.

Conclusion

Clusters of risk factors relate to increased common CIMT in a graded manner, similar in men, women and across race-ethnic groups. Some clusters seemed more atherogenic than others. Our findings support the notion that cardiovascular prevention should focus on sets of risk factors rather than individual levels alone, but may prioritize within clusters.

Introduction

Coronary heart disease and stroke are among the largest contributors of years of life lost and disability adjusted life years in both developed and developing countries [1]. The burden of cardiovascular events is to a large extent preventable through modification of cardiovascular risk factors [2,3]. Risk factors such as elevated blood pressure, smoking, overweight and elevated total cholesterol have been identified as being among the top ten factors responsible for loss of disability adjusted life years [1]. Atherosclerosis underlies the occurrence of a major part of the cardiovascular burden[4]. The development of atherosclerosis starts at a young age, and slowly progresses with ageing [5]. Prevention of the development and progression of atherosclerosis therefore may prevent cardiovascular events from occurring. There is a wealth of evidence supporting the relation of a single risk factor level with presence and extent of atherosclerosis. Although we know that risk factors tend to cluster within individuals [6], studies addressing the relation between clusters of risk factors and atherosclerosis are limited [7], most dealing with the metabolic syndrome as a cluster. Yet, some risk factor clusters may be more atherogenic than others, and the importance of the clusters may vary across groups of individuals, which then may lead to different approaches to prevent cardiovascular disease, in particular when resources are limited. We assessed the relation between clusters of two, three, or four risk factors and atherosclerosis, as measured by common carotid intima-media thickness, in the general population, and compared these relations between men and women, and across race-ethnic groups.

Methods

Study population

The present cross-sectional analyses are based on baseline data from the cohort participating in the USE-IMT collaboration, an individual participant data meta-analysis established to determine the incremental value of measuring common carotid intima media thickness (CIMT) in predicting cardiovascular events [8]. Population-based prospective cohort studies with data on cardiovascular risk factors, common CIMT, and follow-up for cardiovascular events were identified through systematic literature search and expert recommendation. In the current analysis, we included 59,025 individuals from 14 studies (Table 1) [9–22]. Race-ethnic groups were categorised as White, Black, Hispanic or Asian.[23] Diabetes mellitus was defined using the definitions of the individual cohorts, that is using questionnaire information, and /or

Table 1. Baseline characteristics of USE-IMT cohorts in the present analysis.

Study	Individuals	Age (years)	Gender(% male)	Mean CIMT (mm)	BMI (kg/m2)	Smoking (% yes)	SBP (mmHg)	DBP (mmHg)	TC (mmol/L)	HDL (mmol/L)	LDL (mmol/L)	Glucose (mmol/L)
Malmo	5163	57.5 (5.9)	40.5	0.77 (0.15)	25.6 (3.8)	22.5	141 (19)	87 (9)	6.2 (1.1)	1.4 (0.4)	4.2 (1.0)	5.2 (1.4)
CAPS	5056	50.1 (13.1)	48.9	0.73 (0.16)	26.6 (4.1)	20.9	128 (17)	77 (10)	5.7 (1.1)	1.5 (0.4)	3.4 (0.9)	NA
KIHD	1399	52.4 (6.4)	100.0	0.78 (0.18)	26.6 (3.5)	40.1	132 (17)	88 (10)	5.8 (1.0)	1.3 (0.3)	3.9 (1.0)	4.7 (1.3)
ARIC	15732	54.2 (5.7)	44.8	0.66 (0.15)	27.7 (5.4)	26.2	121 (19)	74 (11)	5.6 (1.1)	1.3 (0.4)	3.6 (1.0)	6.0 (2.3)
Virginia	741	56.9 (12.3)	54.8	0.82 (0.18)	26.4 (4.6)	7.3	139 (19)	84 (11)	5.8 (1.3)	1.2 (0.4)	3.7 (1.1)	NA
Tromso	6687	60.2 (10.2)	49.4	0.79 (0.16)	26.0 (4)	31.8	145 (23)	83 (13)	6.8 (1.3)	1.5 (0.4)	4.9 (1.2)	4.9 (1.3)
FATE	1578	49.4 (9.9)	99.7	0.72 (0.18)	28.5 (3.6)	12.0	128 (17)	82 (10)	5.3 (1.0)	1.2 (0.3)	3.3 (0.9)	5.3 (1.0)
OSACA2	769	65.8 (9)	59.2	0.91 (0.31)	23.1 (3.1)	23.3	137 (19)	79 (12)	5.4 (0.9)	1.5 (0.4)	3.0 (0.7)	5.9 (1.7)
MESA	6814	62.2 (10.2)	47.2	0.76 (0.18)	28.3 (5.5)	13.1	127 (21)	72 (10)	5.0 (0.9)	1.3 (0.4)	3.1 (0.8)	5.4 (1.7)
Hoorn	647	70.0 (6.5)	48.8	0.87 (0.17)	27.3 (4)	15.5	142 (21)	83 (11)	5.7 (1.0)	1.4 (0.4)	3.6 (0.9)	6.2 (1.4)
EAS	1115	69.0 (5.6)	49.8	0.77 (0.28)	25.6 (3.8)	18.8	147 (24)	82 (12)	7.1 (1.3)	1.5 (0.4)	5.3 (1.2)	5.8 (1.3)
NOMAS	1770	69.4 (9.3)	39.9	0.73 (0.09)	28.1 (5)	16.1	141 (20)	83 (11)	5.2 (1.0)	1.2 (0.4)	3.3 (0.9)	5.7 (2.4)
NBS	1246	60.7 (5.8)	46.5	0.83 (0.11)	26.5 (3.9)	16.1	128 (15)	78 (10)	5.9 (1.0)	1.4 (0.4)	3.8 (0.9)	5.2 (0.9)
Whitehall	10308	61.1 (6.0)	66.9	0.79 (0.16)	26.8 (4.4)	8.5	128 (17)	74 (11)	5.7 (1.0)	1.6 (0.5)	3.5 (1.0)	NA
Combined	59025	58.0 (9.6)	52.5	0.74 (0.17)	27.0 (4.7)	20.5	130 (21)	77 (11)	5.8 (1.2)	1.4 (0.4)	3.7 (1.1)	5.5 (1.8)

ARIC: Atherosclerosis Risk in Communities Study; CAPS: Carotid Atherosclerosis Progression Study; EAS: Edinburgh Artery Study; FATE: The Firefighters and Their Endothelium Study; Hoorn: The Hoorn Study; KIHD: Kuopio Ischaemic Heart Disease Risk Factor Study; MESA; Multi-race/ethnic Study of Atherosclerosis; NBS: Nijmegen Biomedical Study 2; NOMAS: Northern Manhattan Study; OSACA2: Osaka Follow-Up Study for Carotid Atherosclerosis 2; Tromso: Tromso Study; Whitehall: Whitehall II Study; CIMT: mean common carotid intima media thickness; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

use of blood glucose lowering medication or fasting or casual glucose level.[24] For the definition of history of cardiovascular disease, study-specific definitions were used[8].

Cardiovascular risk factor definition

Methods of measurement of baseline risk factors have been described in previous studies[9–22]. Smoking status was ascertained from self-report questionnaires and defined as current smoking. For each individual, body mass index (BMI) was calculated from measured body weight (in kilograms) divided by measured height (in meters) squared. Overweight was defined as having a BMI ≥ 25 kg/m^2 [25]. Elevated blood pressure was defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90mmHg[26], and elevated cholesterol was defined as total cholesterol ≥ 6.2 mmol/L[27], irrespective of the use of medication. Clusters with diabetes were not included due to the low prevalence (8.5%) in this study population. Based on these risk factors, we defined 15 separate groups ranging from no risk factor present, one risk factor present (only high BP, only smoking, only high cholesterol, only overweight), two risk factors (BP-smoking; BP-overweight; overweight-smoking; cholesterol-overweight; cholesterol-smoking; cholesterol-blood pressure), three risk factors (cholesterol-BP-smoking; overweight-BP-smoking; cholesterol-overweight-BP; cholesterol-overweight-smoking) and four risk factors present (cholesterol-overweight-BP-smoking).

Common carotid intima-media thickness

For each cohort, average mean common CIMT was calculated for each individual using the maximum information of measurements from carotid angles, near and/or far wall measurements, and left and or right side measurements.[8]. Incomplete data on common CIMT, cardiovascular risk factors, and (time to) events resulted in 12% missing data points, which were imputed using single imputation for each cohort separately (using the Multivariate Imputation by Chained Equations package of R). Predictors in our imputation model included all variables in our database including the outcome of interest, as recommended previously [23].

Statistical analysis

We applied a general linear regression model to estimate mean differences in common CIMT with 95% confidence intervals associated with risk factor clusters, adjusted for age, sex, diabetes mellitus, and history of CVD. Main results are additionally presented by sex and race-ethnicity. Potential differences in cluster relations between sexes, race-ethnic groups and age groups ($<$65y, 65-74y; $<$75) was evaluated using a multiplicative interaction term.

Results

Our analysis included 59,025 individuals (47% women), originating from 14 cohorts. Overall, mean age was 58 years, 7% reported a previous history of cardiovascular disease, and 8,5% had diabetes. This group consisted of 46,377 Whites, 6876 Blacks, 2,206 Asians, and 2,575 Hispanics. The prevalence of elevated blood pressure was 33%, of elevated total cholesterol 67%, of overweight 64%, and of smoking 20% (Table 1). Mean common CIMT was 0.74 mm. Of the entire cohort, 14% had no risk factor, 38% one, 32% two, 14% three risk factors and 2% four risk factors.

The common CIMT increased with the number of risk factors present (Fig 1). Compared to those with no risk factors, those with one risk factor had a higher common CIMT (mean difference 0.026 mm (95%CI; 0.022, 0.030). For those with two, three and four risk factors, the increase in common CIMT was 0.052 mm (95%CI; 0.048,0.056), 0.074 mm (95%CI;
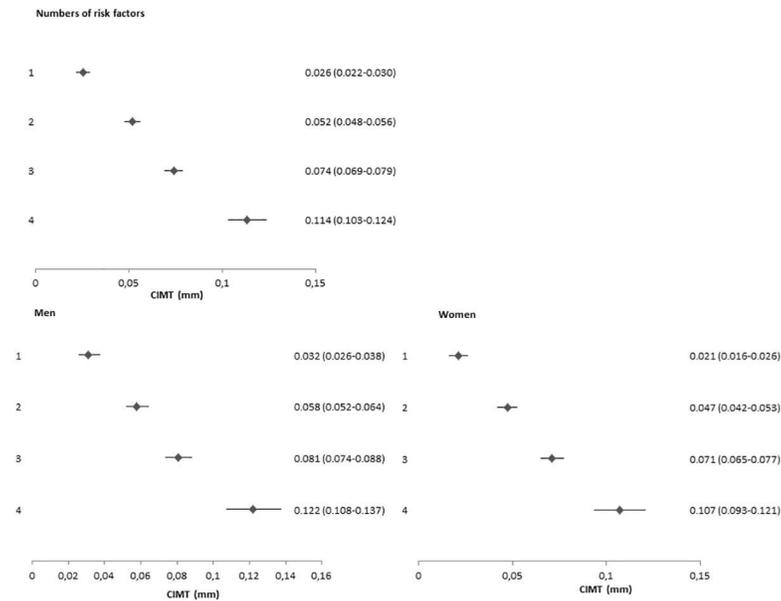
Fig 1. Relation between numbers of risk factors and difference in CIMT (Overall and by sex). Each number of risk factors was compared to individuals without any risk factor (reference group). CIMT, mean common carotid intima media thickness.

0.069,0.079) and 0.114 mm (95%CI; 0.103,0.124), respectively. Similar patterns were seen for men and women (Fig 1) and across race-ethnic groups (Fig 2).

Discussion

This study with 59,025 individuals found that clusters of modifiable risk factors act on common CIMT in a graded manner, in both men and women and across race-ethnic groups. The arterial wall thickness of people with multiple risk factors was generally higher than the sum of the parts, indicative of synergetic effects. Clusters including elevated blood pressure contributed most to the extent of atherosclerosis as measured with common CIMT.

Various national and international cardiovascular risk factor management guidelines promote assessment of absolute event risk based on a set of risk factors, and the absolute risk estimate drives the initiation of preventive therapy [28–30]. We expand that evidence base by showing the relevance of single and combined risk factor information with respect the extent of presence of atherosclerosis, i.e., the higher the CIMT value, the more extensive the atherosclerosis elsewhere in the arterial system [31,32]. Our study is in line with numerous population-based and hospital based studies which have shown graded relations between elevated levels of single modifiable risk factors and increased CIMT [33]. We have shown a graded relation when the burden of several risk factors increases, a finding similar for men as for women and similar across race-ethnic groups. Studies that addressed clustering of risk factors almost exclusively looked into the aspects of the metabolic syndrome, and showed increased CIMT within those with a metabolic syndrome. In contrast, we showed that some clusters have a more adverse effect on the development of atherosclerosis than others. Confirmation of the relation of several clusters with clinical events in this sense may be of great relevance to CVD prognosis.

The main impact of our findings is a further underpinning of the necessity of prevention of the development of key cardiovascular risk factors in order to address the ongoing and
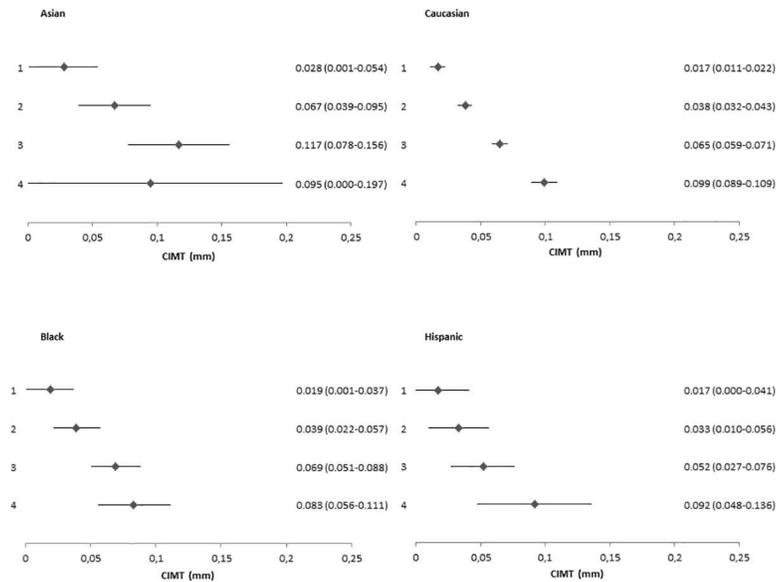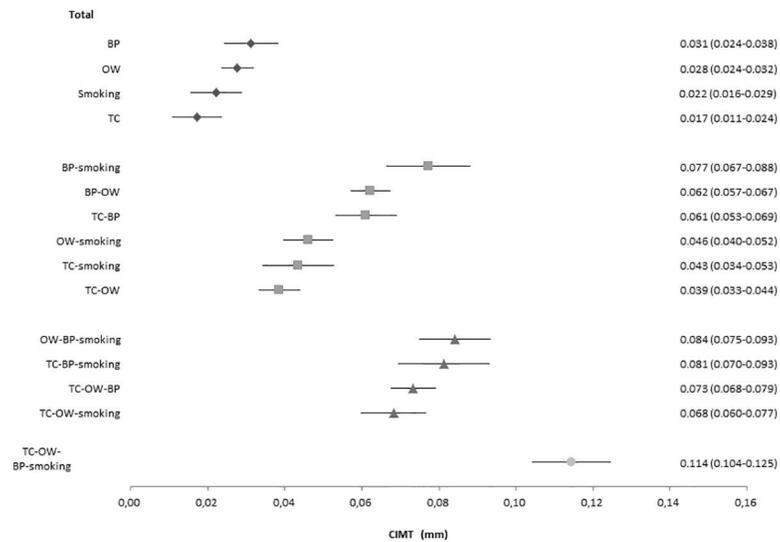
Fig 2. Relation between numbers of risk factors and differences in CIMT by race-ethnic group. Each number of risk factors was compared to individuals without any risk factor (reference group). CIMT, mean common carotid intima media thickness. Fig 3 presents the main findings of the overall analysis on risk factor clusters and CIMT. Within each risk factor cluster, there were graded relations with common CIMT. Within those with two risk factors, the cluster blood pressure-smoking had the highest CIMT (mean difference of 0.077 mm with those without risk factors) and the cluster with overweight- total cholesterol the least thickening (mean difference of 0.039 mm with those without risk factors), a difference reaching statistical significance with the cluster since the 95 confidence limits did not overlap. For people within the three risk factor cluster, elevated blood pressure, overweight and smoking had the highest common CIMT (0.084 mm). The pattern of the relationship between risk factor clusters and common CIMT were similar between sexes and race-ethnic groups, although some variation was observed between race-ethnic groups but was not significant due to limited minority samples sizes (S1 and S2 Figs). The interaction terms were not statistically significant.

upcoming cardiovascular epidemic in high income societies and emerging economies, respectively. There is substantial evidence that addressing these modifiable risk factors through statin treatment [34,35], blood pressure treatment [36], smoking cessation[37] or interdisciplinary weight loss therapy[38] lead to halting the progression or even reduce common CIMT and thus slow down development of atherosclerosis. Such evidence complements the effects of risk factor management on reduction on cardiovascular events. Ways to improve cardiovascular health in communities in the future have been recently outlined by Vasan and co-worker pointing towards an approach that includes a full range of biological, environmental and social determinants of cardiovascular health[39]. Prevention strategies should indeed be targeted to the local situation, depending on the risk factor cluster prevalence (e.g. high in China, much lower in The Netherlands[40]), its associated risk with atherosclerosis and clinical events, cultural aspects regarding life style and prevention of the population and budgetary restraints.

The strength of our study comes from the large sample size from multiple cohorts from various parts of the world that collaborate in the ongoing USE-IMT initiative. Moreover, the cohorts in USE-IMT were derived from the general population, which increase the generalizability of our results. Furthermore, we analyzed the values of CIMT for sex and race-ethnic groups separately.

Several limitations should be emphasized when interpreting the results. First of all, due to the cross-sectional design we need to be cautious with causal interpretation. Yet, an increased CIMT at a certain age is viewed as the reflection of life long exposure to the cardiovascular risk

Fig 3. Relation between risk factor clusters and differences in CIMT (Overall). Each cluster was compared to individuals without any risk factor (reference group). CIMT, mean common carotid intima media thickness. BP, elevated blood pressure; OW, overweight; TC, elevated total cholesterol; smoking, current smoking.For most of the risk factors, the sum of the individual risk factor differences was smaller than the observed mean difference for the cluster in the overall analyses. For example, the mean difference in common CIMT for the blood pressure—smoking cluster was 0.077 mm, whereas the sum of the individual risk factors was 0.053 (i.e., 0.031 + 0.022). A similar finding was found for the smoking-blood pressure-overweight cluster. This observation suggests synergetic effects of risk factors on CIMT.

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factors. Also, it is well established that elevated blood pressure, smoking, overweight and elevated total cholesterol contributes to cardiovascular disease[1]. Furthermore, several reviews showed the beneficial effects of lipid lowering and blood pressure lowering on progression of common CIMT [41,42]. Secondly, one may argue that common CIMT in itself does not reflect atherosclerosis[43]. The measurement of common CIMT is, however, used as a reflection of atherosclerosis in the coronary arteries [44], the abdominal aorta [45], the arteries of the lower extremities, and in the carotid bifurcation and internal carotid artery [46]. In addition, common CIMT is a reflection of cardiovascular risk, as many studies have shown that increased common CIMT relates to an increased risk of cardiovascular events in the future [8]. Thirdly, the protocols to assess and measure mean common CIMT varied by the studies. This may have led to an increased variability of the common CIMT measurement and thus an underestimation of the relations under study.

In conclusion, clusters of modifiable risk factors are related to increased common CIMT, as an indicator of the extent of atherosclerosis, in a graded manner, similar in men, women and across race-ethnic groups. Some clusters seemed more atherogenic than others. Our findings support the notion that cardiovascular prevention should focus on sets of risk factors rather than individual levels alone, but may prioritize within clusters.

Supporting information

S1 Fig. Relation between risk factor clusters and CIMT (by sex). Each cluster was compared to individuals without any risk factor (reference group). CIMT, mean common carotid intima media thickness. BP, elevated blood pressure; OW, overweight; TC, elevated total cholesterol; smoking, current smoking.
(TIF)

S2 Fig. Relation between risk factor clusters and CIMT (by race-ethnic group). Each cluster was compared to individuals without any risk factor (reference group). CIMT, mean common carotid intima media thickness. BP, elevated blood pressure; OW, overweight; TC, elevated total cholesterol; smoking, current smoking.
(TIF)

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