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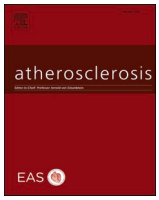

Occurrence of coronary events in the absence of traditional risk factors: Understanding residual risk

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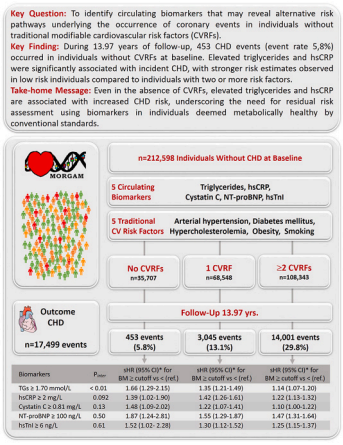
HIGHLIGHTS

- Determinants of incident CHD in individuals without traditional CV risk factors (CVRFs) remain poorly understood.
- Elevated triglycerides and hsCRP were significantly associated with an increased CHD risk even in CVRF-free individuals.
- Biomarker-based assessment reveals residual CHD risk in individuals, deemed metabolically healthy by conventional standards.

GRAPHICAL ABSTRACT



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ABSTRACT

Background and aims: The major predictors of future coronary heart disease (CHD) events in individuals without traditional modifiable cardiovascular risk factors (CVRFs) remain unknown. We investigated the association between circulating biomarkers, reflecting residual risk, with incident CHD in a general population, according to the presence of five CVRFs (hypertension, diabetes mellitus, hypercholesterolemia, smoking and obesity) at baseline.

Methods: Overall 212,598 CHD-free individuals from 21 European population-based cohorts were stratified by CVRF burden into three groups, having zero (n = 35,707), one (n = 68,548) or ≥2 (n = 108,343) risk factors at baseline. Five biomarkers (triglycerides (TGs), high-sensitivity C-reactive protein (hsCRP), cystatin C, N-terminal pro-B-type natriuretic peptide and high-sensitivity troponin I) were assessed in a subset with available measurements.

Results: During a median follow-up of 13.97 years, 17,499 participants developed incident CHD with 453 events occurring among individuals without CVRFs. Although increased concentrations of all biomarkers were related to incident CHD, significant risk modulation by CVRFs was seen only for TGs and, to a lesser extent, for hsCRP. The fully-adjusted sub-distribution Hazard Ratios (95 % CI) were for TGs (≥vs < 1.70 mmol/L) 1.66 (1.29–2.15) in those without CVRFs versus 1.35 (1.21–1.49)/1.14 (1.07–1.20) in those with 1 or ≥2 risk factors ($p_{interaction}$<0.01) and for hsCRP (≥vs < 2 mg/L) 1.39 (1.02–1.90) versus 1.42 (1.26–1.61) or 1.22 (1.13–1.32), respectively ($p_{interaction}$ = 0.092).

Conclusion: Even in the absence of CVRFs, elevated triglycerides and hsCRP were significantly associated with an increased risk of CHD. These results highlight the importance of residual risk assessment using those biomarkers in individuals deemed metabolically healthy by conventional standards.

1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) is a potentially preventable and treatable group of conditions, which remains a leading cause of morbidity and mortality [1,2]. Recent data from the Global Cardiovascular Risk Consortium (GCVRC), including 1,518,028 participants from 112 cohorts, revealed that 57.2 % of all incident CVD events in women and 52.6 % in men over a median follow-up of ~10 years were attributable to five major cardiovascular risk factors [3]. However, these findings also highlight that there is still a significant proportion of events that are not explained by them. This suggests the presence of competing or alternative risk pathways [4] that might become clinically relevant only in the absence of modifiable cardiovascular risk factors (CVRFs) and thereby reflects an unmet need for a deeper understanding of the underlying pathophysiology of atherosclerosis. In line with this are data from the Progression of Early Subclinical Atherosclerosis (PESA) study, which impressively showed that even in the absence of modifiable risk factors up to 50 % of all study participants already had subclinical atherosclerosis by imaging [5]. Also, in the setting of an acute coronary syndrome it is well known that up to 20 % of patients presenting with a first coronary event do not report any CVRFs on admission [6–9]. More importantly, these individuals even had a substantially higher in-hospital mortality rate compared to those with one or more risk factors [7–10]. Therefore, further research is urgently needed to reveal still undiscovered mechanisms that might contribute to the development of ASCVD in those individuals. Given the high prevalence of apparently healthy CVRF-free individuals in the general population (up to 20 %), even a low individual risk could lead to a significant number of cardiovascular events at a population level.

From this public health perspective, it is therefore important to evaluate whether certain risk modifiers, such as e.g. high-sensitivity C-reactive protein (hsCRP) or other emerging circulating biomarkers could

[1] contributed equally.

Abbreviation

ASCVD = Atherosclerotic cardiovascular disease
BiomarCaRE = Biomarker for Cardiovascular Risk Assessment across Europe
CHD = coronary heart disease
CVRFs = cardiovascular risk factors
GCVRC = Global Cardiovascular Risk Consortium
hsCRP = high sensitivity C-reactive protein
MORGAM = MOnica Risk, Genetics, Archiving and Monograph
NT-proBNP = N-terminal pro-B-type natriuretic peptide
SD = standard deviation
SMuRFs = Standard Modifiable cardiovascular Risk Factors
TG = triglycerides
hsTnI = high-sensitivity troponin I

explain at least some of the events occurring among individuals without CVRFs. Although it is well established that biomarkers predict future CHD risk in general, to date large-scale, rigorous evaluation of biomarker-associated risk in this very low-risk population is still lacking, thereby representing a significant gap in the current literature.

Therefore, the aim of the present analysis was to investigate the association between baseline concentrations of different cardiometabolic biomarkers and the risk of future CHD events in individuals from the general population across the spectrum of CVRF burden at the time of enrollment. Furthermore, we also aimed to evaluate whether the magnitude of this association differs between CVRF-free individuals and those with the presence of traditional risk factors at baseline. This could help to identify possible novel targets for preventive strategies to address the increased CHD risk in this specific low risk population.

2. Material and methods

2.1. Study design, population and outcome

The present investigation included 21 population-based cohorts, participating in the European MOnica Risk, Genetics, Archiving and Monograph (MORGAM) (https://www.thl.fi/morgam/) and the Biomarker for Cardiovascular Risk Assessment across Europe (BiomarCaRE) (http://biomarcare.eu/) consortia. Details of both consortia have been published elsewhere [11,12]. All cohorts obtained approval by the responsible local ethical review boards. Participation was voluntary and written informed consent was obtained from each subject upon entry into the study. This study was performed according to the principles of Good Clinical Practice and the Declaration of Helsinki.

For analysis, data from cohorts with available baseline information on CVRFs were used, resulting in a total of 240,729 individuals. The detailed cohort descriptions as well as number of participants in each cohort (before any exclusions) are provided in the Supplemental Table 1. After further exclusion of individuals with missing baseline information on CVRFs or CHD status, as well as those with prevalent CHD at baseline, the final study sample comprised 212,598 individuals without CHD: ATBC (n = 25,810); DAN-MONICA (n = 7370); ESTHER (n = 7946); FINRISK (n = 31,558); Kaunas Study (n = 4096); MATISS Study (n = 7884); Moli-Sani Study (n = 22,682); MONICA-Brianza (n = 4544); MONICA-Catalonia (n = 5333); MONICA/KORA (n = 15,659); MONICA-Friuli (n = 5042); MONICA-PAMELA (n = 1875); Northern

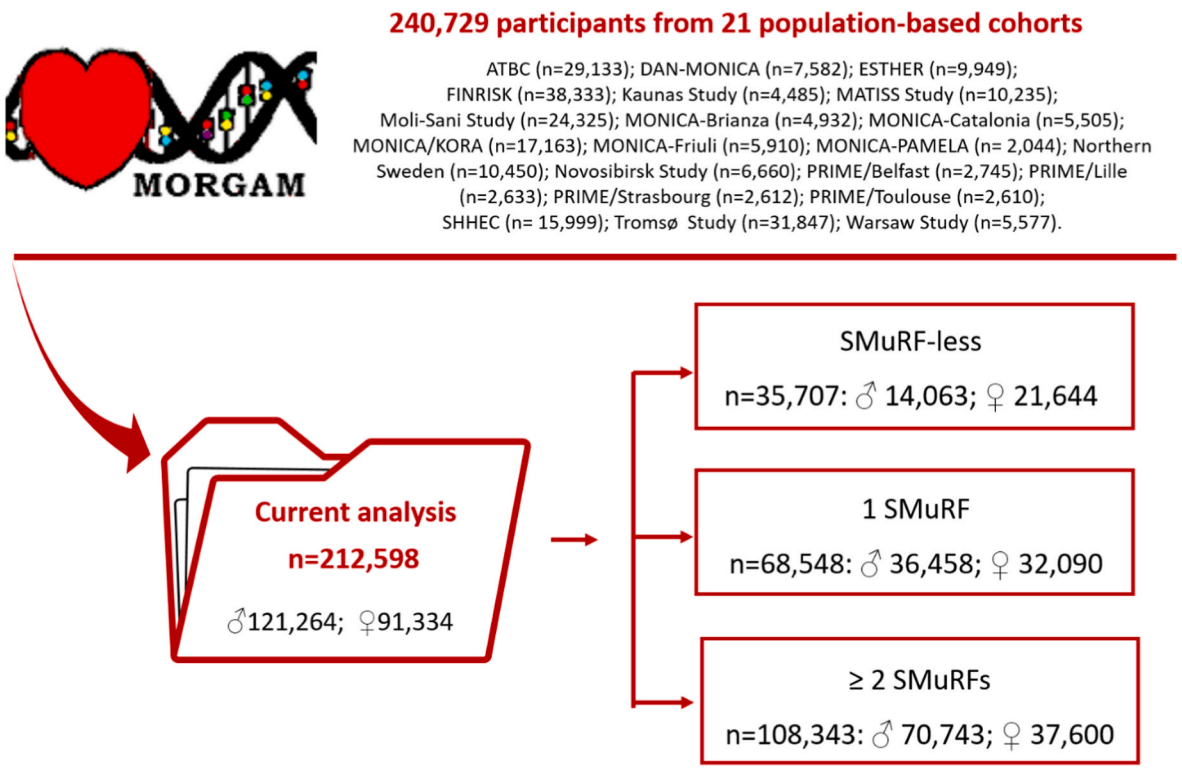

Fig. 1. Flow chart of the study.
ATBC = Alpha-Tocopherol, Beta-carotene Cancer prevention; MONICA = MONItoring of trends and determinants in CArdiovascular diseases; ESTHER = Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung [German]; MATISS = Malattie cardiovascolari ATerosclerotiche, Istituto Superiore di Sanità [Italian]; KORA = KOoperativen Gesundheitsforschung in der Region Augsburg [German]; PAMELA = Pressioni Arteriose Monitorate E Loro Associazioni [Italian]; PRIME= PRospective epIdemiological study of Myocardial Infarction; SHHEC= Scottish Heart Health Extended Cohort; MORGAM = MOnica Risk, Genetics, Archiving and Monograph; CVRFs = cardiovascular risk factor; CHD = coronary heart disease.

Sweden MONICA (n = 9315); Novosibirsk Study (n = 5524); PRIME/Belfast (n = 2398); PRIME/Lille (n = 2232); PRIME/Strasbourg (n = 2273); PRIME/Toulouse (n = 2370); SHHEC (n = 13,970); Tromsø Study (n = 30,467); and the Warsaw Study (n = 4250). A flowchart of the study is presented in Fig. 1.

All individuals were prospectively followed for incident CHD, defined as fatal or non-fatal (definite or possible) myocardial infarction (MI) and/or coronary death, unstable angina pectoris, cardiac revascularization (the last two were not available for MONICA/KORA Augsburg), as well as unclassifiable death (i.e. death with insufficient evidence of coronary origin and no competing cause). Most centers adjudicated the events using MONICA diagnostic criteria. The description of the MORGAM Cohorts provides further information on the endpoint classification in each cohort [13].

2.2. Data collection and risk factor definition

For detailed information on data collection and risk factor definition please see the **online data Supplement.** For the analyses, all study participants were stratified into having "0", "1" and "≥2" of the following risk factors: arterial hypertension, diabetes mellitus, hypercholesterolemia, obesity and daily smoking at baseline. For better comparability with previous investigations [8–10] we used a widely accepted definition of standard modifiable cardiovascular risk factors (SMuRFs), but further extended it and included obesity and other clinical variables firstly to cover similar risk factors that were used within the Global Cardiovascular Risk Consortium [3] and secondly to ensure their more comprehensive assessment at baseline. Arterial hypertension was defined as systolic blood pressure (BP) ≥140 mmHg and/or diastolic BP ≥ 90 mmHg, or the use of antihypertensive medication. Diabetes mellitus was defined as a documented or self-reported history of diabetes or the use of glucose-lowering medications. Hypercholesterolemia was defined as total cholesterol (TC) ≥5.5 mmol/L (≥210 mg/dL) or low-density lipoprotein cholesterol (LDL-C) ≥3.5 mmol/L (≥135 mg/dL) or use of lipid-lowering medication, obesity as a body mass index (BMI) ≥ 30 kg/m^2 and smoking as "daily smoking".

2.3. Laboratory measurements

For the present analysis, various biomarkers of interest were selected, based on their possible involvement in the pathogenesis of CHD [4,14], reflecting metabolic, inflammatory, renal or cardiac-function related risk as well as on their availability within the BiomarCaRe population. Most of the biomarkers were measured from stored blood samples in the central BiomarCaRE laboratory in either Mainz (until 2011) or after the transfer of the biobank (since 2011) to the University Medical Center Hamburg-Eppendorf in Hamburg, Germany. Triglycerides (TGs) were measured either locally at each participating center by routine methods or in the BiomarCaRE central laboratory. Biomarkers were available only in a subset of cohorts (TGs n = 140,182; hsCRP n = 85,229; cystatin C n = 73,431; N-terminal pro-B-type natriuretic peptide (NT-proBNP) n = 60,160; high-sensitivity troponin I (hsTnI) n = 73,779). HsCRP was measured on an Abbott Architect c8000 system using the latex immunoassay (CRP Vario CRP16, Abbott Diagnostics, USA, ARCHITECT c8000) with intra-assay and inter-assay coefficients of variation of 0.93 and 0.83 [15]. Cystatin C was measured by an immunoassay on an Abbott ARCHITECT platform [16]. NT-proBNP levels were measured on an ELECSYS 2010 or a Cobas e411 using an electrochemiluminescence immunoassay (ECLIA, Roche Diagnostics) with an analytical range of 5–35,000 ng/L and intra-assay and inter-assay coefficients of variation of 2.58 % and 1.38 % [14,17]. Hs-TnI was measured using an immunoassay (Abbott Diagnostics, USA, ARCHITECT i2000SR) with a limit of detection of 1.9 ng/L (range 0–50,000 ng/L). Coefficients of variations for intra-assay and inter-assay testing were 4.26 % and 6.29 %, respectively [17,18].

2.4. Statistical analysis

Baseline characteristics of the study participants are reported descriptively and shown as frequencies (percentage) for binary variables and as medians with 25th and 75th percentiles for continuous variables. Spearman rank correlation coefficients were calculated to assess the correlation between the biomarkers of interest.

The median follow-up times and event rates were estimated by the Kaplan-Meier potential follow-up estimator [19]. Event rates were calculated for the complete follow-up time.

To identify possible determinants of CHD events in those with no, one or ≥2 traditional CVRFs at baseline, Fine and Gray models accounting for the competing risk of death from a non-CHD cause, stratified by the study cohort were calculated. An interaction term between the biomarker of interest and the CVRF groups was also included in the regression models.

For the present analysis biomarkers were assessed as dichotomous variables, using either recently proposed cut-offs, reflecting residual cardiovascular risk [4], being 2 mg/L for hsCRP (<2$^{ref.}$ vs ≥ 2 mg/L) and 1.70 mmol/L (150 mg/dL) for TG (<1.70$^{ref.}$ vs ≥ 1.70 mmol/L). For hsTnI, a cut-off of 6 ng/L (<6$^{ref.}$ vs. ≥6 ng/L), as suggested by our previous analysis [17] was used. For NT-proBNP a cut-off of 100 ng/L (<100$^{ref.}$ vs. ≥100 ng/L) was used. For cystatin C, the cohort specific medians were applied as cut-offs. Within the second step (sensitivity analysis), each biomarker of interest was included as a continuous variable (per standard deviation (SD) increase) in the regression models. Cystatin-C was cubic-root transformed, whereas hsCRP, TGs, NT-proBNP, and hsTnI were log-transformed. In both analyses, similar levels of adjustment were used. Model 1 was adjusted for age, sex and fasting status. Model 2 was additionally adjusted for systolic BP, diabetes mellitus, BMI, daily smoking and for LDL-C. The results are presented as sub-distribution Hazard Ratios (sHRs) with their 95 % confidence interval (95 % CI). Finally, to visualize the association between the biomarkers of interest (as a continuous variable) with outcome, all biomarkers were modelled using restricted cubic splines after adjustment for the same variables, as performed in the fully adjusted model 2. In addition, a winsorization was applied to reduce the impact of outliers. All plots were created with the function *visreg*().

R version 4.2.2 software (R Foundation for Statistical Computing, Vienna, Austria) was used to perform all statistical analyses.

3. Results

3.1. Study population

Overall, 212,598 individuals from 21 prospective population-based cohorts (median age 50.6 (IQR 39.2–58.1) yrs.; 57 % male), who were free of CHD at the time of enrollment, were included in the present analysis. Of CHD-free individuals, 16.8 % were free of CVRFs at baseline (n = 35,707), whereas 68,548 participants (32.2 %) had one and 108,343 participants (51.0 %) had two or more CVRFs at baseline.

The baseline demographic and clinical characteristics of study participants are presented in Table 1. In general, individuals without CVRFs at baseline were younger than individuals with CVRFs, predominantly female, demonstrated higher levels of education and consumed less alcohol (Table 1). Furthermore, they had lower systolic BP, favorable anthropometric measures (BMI/waist circumference) and had a lower prevalence of a family history of CHD. Supplemental Table 2 demonstrates the baseline characteristics of the study participants, stratified by study center.

Concentrations of almost all biomarkers increased proportionally to the number of CVRFs, being the lowest in those without risk factors and the highest in individuals reporting two or more CVRFs at baseline (Table 1). In contrast, median values of cystatin C were similar among all three CVRF categories. Baseline biomarkers' distribution by applied cut-offs as well as Spearman rank correlation coefficients between

Table 1
Baseline demographic, clinical and laboratory characteristics of the study participants.

	All	0 CVRFs	1 CVRF	≥2 CVRFs
N	212,598	35,707	68,548	108,343
Examination age, (years)	50.6 (39.2–58.1)	39.2 (31.0–48.4)	46.7 (36.2–55.8)	54.3 (46.5–60.6)
Male, %	57.0	39.4	53.2	65.3
Systolic BP, (mmHg)	132.0 (120.0–146.0)	120.5 (113.0–129.0)	126.0 (117.0–136.0)	142.0 (130.0–155.5)
BMI, (kg/m^2)	25.7 (23.2–28.6)	23.7 (21.8–26.0)	24.9 (22.7–27.3)	27.1 (24.4–30.6)
Waist circumference, (cm)	89.5 (80.5–98.0)	81.0 (74.0–89.0)	87.0 (79.0–95.0)	95.0 (87.0–103.5)
Daily alcohol consumption, (g)	6.0 (0–21.0)	4.0 (0–14.0)	5.0 (0–20.0)	7.0 (0–25.0)
Highest level of education, %[a]	13.6	24.3	15.9	8.6
Family history of CHD, %	20.5	16.7	19.8	22.8
Hypertension, %	40.2	0.0	18.8	67.0
Diabetes mellitus, %	3.6	0.0	0.9	6.5
Hypercholesterolemia, %	57.1	0.0	45.7	83.1
Daily smoker, %	38.0	0.0	29.0	56.3
Obesity, %	17.1	0.0	5.6	30.1
Medication				
Lipid-lowering drugs, %	3.5	0.0	1.9	6.2
Antihypertensive drugs, %	10.8	0.0	4.9	19.9
Laboratory parameters				
LDL-C, mmol/L	3.5 (2.9–4.2)	2.8 (2.4–3.2)	3.4 (2.8–4.1)	4.0 (3.5–4.6)
Triglycerides, mmol/L	1.2 (0.9–1.8)	0.9 (0.7–1.2)	1.1 (0.8–1.6)	1.5 (1.1–2.1)
hsCRP, mg/L[b]	1.4 (0.6–3.0)	0.8 (0.4–1.8)	1.1 (0.6–2.3)	1.9 (0.9–3.9)
Cystatin C, mg/L[b]	0.8 (0.7–1.0)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.9 (0.8–1.0)
NT-proBNP, ng/L[b]	43.9 (23.6–80.3)	40.6 (23.1–69.8)	41.5 (22.8–74.4)	48.0 (24.5–91.6)
hsTroponin I, ng/L[b]	2.3 (1.4–3.9)	1.6 (0.9–2.6)	2.2 (1.3–3.6)	2.8 (1.8–4.6)

Data are presented as median with their interquartile range for continuous variables. Categorical variables are reported as percentages. BP = blood pressure; BMI = body mass index; CHD = coronary heart disease; CVRF = cardiovascular risk factor; HDL = high density lipoprotein; LDL = low density lipoprotein; C = cholesterol; hsCRP = high sensitivity C-reactive protein; NT-proBNP = N-terminal pro B-type natriuretic peptide. [a]University study; [b]measured only in subcohorts.

biomarkers of interest are presented in the Supplemental Table 3 and Supplemental Fig. 1, respectively.

3.2. CHD event rates by CV risk burden

During a median follow up time of 13.97 yrs. 17,499 study participants of the entire cohort (n = 212,598) developed an incident CHD event (event rate: 20.0 %). Among them, 453 events (5.8 %) were observed among individuals without CVRFs at baseline. In contrast, 3045 CHD events (13.1 %) occurred in individuals with one and 14,001 events (29.8 %) in those with two or more risk factors at baseline.

3.3. Association between circulating biomarkers and incident CHD

3.3.1. Triglycerides

Among individuals without CVRFs at baseline, increased TG concentration (≥1.70 mmol/L or 150 mg/dL, respectively) was strongly associated with future CHD events, resulting in a fully adjusted sHR (95

Table 2
Association between circulating biomarkers and risk of incident CHD, according to the presence of traditional risk factors.

	0 CVRFs				1 CVRF				≥2 CVRFs				P_{inter}[a]
	$N_{overall}$	N_{events}	sHR (95 % CI)	p-value	$N_{overall}$	N_{events}	sHR (95 % CI)	p-value	$N_{overall}$	N_{events}	sHR (95 % CI)	p-value	
Triglycerides													
<1.70 mmol/L	20,594	200	REF.		33,141	1023	REF.		34,969	2582	REF.		
≥1.70 mmol/L	2738	81	1.66 (1.29–2.15)	<0.001	9329	580	1.35 (1.21–1.49)	<0.001	20,512	2280	1.14 (1.07–1.20)	<0.001	<0.01
hsCRP													
<2 mg/L	10,394	131	REF.		17,636	643	REF.		16,695	1261	REF.		
≥2 mg/L	3045	56	1.39 (1.02–1.90)	0.036	7485	414	1.42 (1.26–1.61)	<0.001	15,807	1538	1.22 (1.13–1.32)	<0.001	0.092
Cystatin C													
< Median	7631	62	REF.		10,496	287	REF.		9355	530	REF.		
≥ Median	4410	108	1.48 (1.09–2.02)	0.013	11,743	702	1.22 (1.07–1.41)	0.0043	19,031	2082	1.10 (1.00–1.22)	0.049	0.13
NT-proBNP													
<100 ng/L	8936	92	REF.		15,443	509	REF.		18,292	1180	REF.		
≥100 ng/L	1372	30	1.87 (1.24–2.81)	0.0026	2929	151	1.55 (1.29–1.87)	<0.001	5231	526	1.47 (1.31–1.64)	<0.001	0.50
hsTroponin I													
<6 ng/L	11,635	141	REF.		20,370	729	REF.		23,869	1661	REF.		
≥6 ng/L	684	27	1.52 (1.02–2.28)	0.042	2165	213	1.30 (1.12–1.52)	<0.001	4499	808	1.25 (1.15–1.37)	<0.001	0.61

Fine and Gray competing risk-adjusted models stratified by study cohort were calculated and the data are presented as sub-distribution hazard ratios (sHRs) with their 95 % confidence interval (95 % CI).
CVRF = cardiovascular risk factor; hsCRP = high sensitivity C-reactive protein; NT-proBNP = N-terminal pro B-type natriuretic peptide; BMI = body mass index; LDL = low density lipoprotein; C = cholesterol.
Models adjusted for examination age, fasting status, male sex, systolic blood pressure, diabetes mellitus, BMI, daily smoking and LDL-C.
[a] P values for interactions across CVRF categories.

% CI) of 1.66 (1.29–2.15) ($p < 0.001$). Of note, the magnitude of the "TG - outcome" association decreased with increasing numbers of risk factors: the corresponding sHRs (95 % CI) were 1.35 (1.21–1.49) and 1.14 (1.07–1.20) in individuals with 1 or ≥2 CVRFs, respectively (p for interaction between three groups <0.01) (Table 2, Supplemental Table 4). Additional adjustment for daily alcohol intake did not change the results significantly (data not shown). Similar results were seen when TG concentrations were used as a continuous variable with sHRs (95 % CI) of 1.34 (1.18–1.52) in CVRF-free individuals versus 1.26 (1.19–1.33) and 1.13 (1.09–1.17) in individuals with 1 and ≥ 2 risk factors per one SD increase (Fig. 2, Supplemental Table 5) (p for interaction<0.01).

3.3.2. High sensitivity C-reactive protein

The association between increased hsCRP levels (≥2 mg/L) and CHD events was also modulated by CVRFs at baseline, with a stronger association, seen in individuals at low risk (i.e. in CVRFs-free and those with 1 risk factor at baseline) than in subjects with two and more CVRFs. The corresponding sHRs (95 % CI) were 1.39 (1.02–1.90) or 1.42 (1.26–1.61) versus 1.22 (1.13–1.32) for 0, one or ≥2 risk factors, respectively (p for interaction 0.092) (Table 2, Supplemental Table 5). The results of continuous analyses are presented in Fig. 2 or Supplemental Table 5.

3.3.3. Cystatin C

A strong association between increased Cystatin C concentration and incident CHD was observed for individuals without CVRFs at baseline, with a corresponding sHR (95 % CI) of 1.48 (1.09–2.02). By contrast, in those having 1 or ≥2 risk factors, the sHRs were lower, 1.22 (1.07–1.41) and 1.10 (1.00–1.22), respectively ($p_{interaction} = 0.13$) (Table 2, Supplemental Table 4). The sensitivity analysis with Cystatin C as a continuous variable was in line with the results of the dichotomized approach (Fig. 2, Supplemental Table 5).

3.3.4. Cardiac biomarkers

Finally, we evaluated the relationship between two cardiac biomarkers (NT-proBNP and hsTnI) and future CHD events showing that increased concentrations of both were independently associated with incident CHD in all three groups, in both dichotomized and continuous analyses (Table 2, Supplemental Table 4; Fig. 2, Supplemental Table 5). However, no interactions with CVRF burden were observed neither for hsTnI ($p_{interaction} = 0.61$) nor for NT-proBNP ($p_{interaction} = 0.50$). The corresponding sHRs (95 % CI) were 1.87 (1.24–2.81), 1.55 (1.29–1.87) and 1.47 (1.31–1.64) for NT-pro BNP and 1.52 (1.02–2.28), 1.30 (1.12–1.52) and 1.25 (1.15–1.37) for zero, one or ≥2 CVRFs for hsTnI, respectively.

The shape of the association between all biomarkers of interest and incident CHD in accordance with CVRF burden at baseline, estimated by restricted cubic spline regression is graphically presented in Supplemental Fig. 2.

4. Discussion

Recent research has provided a wealth of data indicating that the atherosclerotic process might be triggered or exacerbated by pathways independent of CVRFs. Although awareness has increased in recent years concerning the occurrence of CHD events in the absence of CVRFs [14,20] the determinants of risk in individuals without traditional risk factors have remained unclear. Such uncertainties substantially limit our ability to adequately address risk in those individuals, since almost all

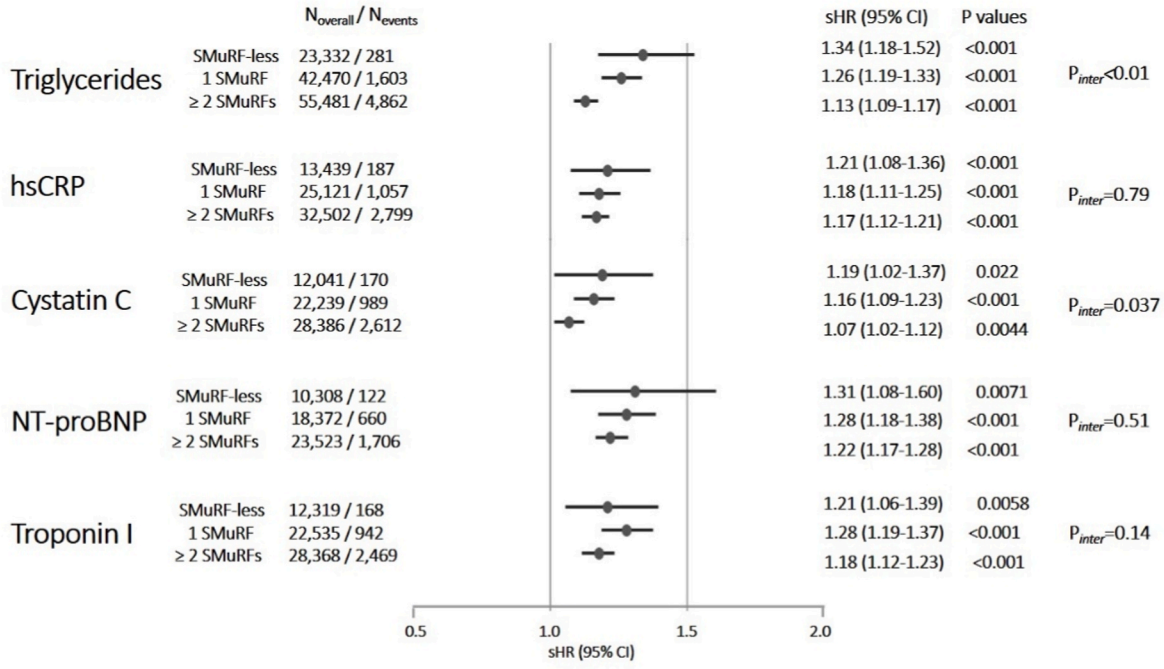

Fig. 2. Association between circulating biomarkers and risk of incident CHD, according to the risk factor burden at baseline: continuous analysis per standard deviation increase

Fine and Gray competing risk-adjusted models stratified by study cohort were calculated and the data are presented as sub-distribution Hazard ratios (sHRs) with their 95 % confidence interval (95 % CI). The following biomarkers were transformed for the analysis: log-transformed (triglycerides, hsCRP, NT-proBNP, troponin I), cubic-root transformed (cystatin C)

Models adjusted for examination age, fasting status, male sex, systolic blood pressure, diabetes mellitus, BMI, daily smoking and LDL-C. P values for interactions across CVRF categories

CVRFs = cardiovascular risk factors; hsCRP = high sensitivity C-reactive protein; NT-proBNP = N-terminal pro B-type natriuretic peptide; BMI = body mass index; LDL = low density lipoprotein; C = cholesterol.

available preventive strategies focus on traditional and potentially modifiable CVRFs, which may not be applicable to these individuals. Therefore, alternative approaches that consider non-traditional risk determinants are urgently needed to close this gap in preventive care.

The present analysis represents the first comprehensive, population-based investigation to quantify biomarker-associated cardiovascular risk among individuals free of the five major modifiable risk factors, offering important evidence on residual risk within a subgroup traditionally considered to be at low risk. More importantly, our findings suggest that CVRF burden at baseline might significantly modulate the "biomarker-outcome" association for TGs and to a lesser extent for hsCRP.

Although the association between increased TG concentration and CVD in general is well known and highly debated to date [21], its strong relationship with incident CHD in this very low risk population of individuals without traditional risk factors represents a novel finding. So far, high TG concentrations have been mainly considered as a hallmark of metabolic (obesity-related or diabetic) dyslipidemia, which is highly sensitive to lifestyle modification [22]. In general, increased TG levels might represent a good indicator/proxy of high levels of the cholesterol content of triglyceride-rich lipoproteins (TRLs), so-called TRL/remnant cholesterol (RC). Of note, several lines of evidence indicate that RC but not TG content itself would explain the association with future atherosclerotic CVD [21,23,24]. Interestingly, in contrast to LDL-C, TRLs and their remnants do not necessarily require any modification to be taken up by macrophages in the intima [25] and therefore might accumulate in their naïve forms. This might represent one possible explanation why increased TGs are related to future CHD events even in the absence of CVRFs, which are well-known as major triggers of LDL-C modification in the subendothelial space (oxidation (by e.g. smoking) or glycation (by e.g. diabetic status)) [26]. Furthermore, high TG values in low-risk individuals might also serve as a proxy for subclinical metabolic dysregulation such as e.g. hepatic VLDL overproduction, or impaired lipolysis—all hallmarks of insulin resistance, which is not captured by traditional CVRFs. More importantly, the high risk of incident CHD, seen among individuals with moderately elevated TGs (≥1.7 mmol/L) [23] but having optimal blood pressure (mean systolic BP 120.5 mmHg), normal weight (mean BMI 23.7 kg/m^2), no signs of abdominal obesity (mean waist circumference 81 cm) or diabetes mellitus as well as much lower daily alcohol consumption than those with the presence of CVRFs might suggest alternative (non-metabolic) pathways of TG atherogenicity (e.g., through the NLRP3 inflammasome activation by apolipoprotein C-III (apoC-III) or binding to coagulation factors VII and X) [21], pointing toward TGs as one of the central mediators of a lipid-inflammatory axis. Furthermore, our findings might also have important therapeutic implications for both clinical practice and future research. While lifestyle modification remains the cornerstone of TG management, emerging therapies, such as apoC-III or ANGPTL3 inhibition, might hold promise due to their dual effect on lowering TGs and RC, and warrant further investigation in this underrecognized population.

Interestingly, the present analysis also showed that even in the absence of five major traditional risk factors, 22.1 % of CVRF-free individuals demonstrated an increased inflammatory burden (i.e. hsCRP ≥2 mg/L), and the association between increased hsCRP concentration and incident CHD in this very low risk population was even numerically stronger than among "high absolute risk" individuals, who had two or more risk factors at baseline. These findings are intriguing, since so far, BMI/obesity in combination with smoking have been considered to be the most important determinants of hsCRP concentration especially in prospective studies [27], thereby highlighting the importance of low-grade inflammation even in very low-risk individuals with optimal cardiometabolic health. The potential significance of such an association is a theoretical option to reduce future CHD risk by targeting residual inflammation through anti-inflammatory agents [28,29]. However, it still remains to be determined whether pharmacological inhibition of inflammation would also result in CVD risk reduction in this particular group. Until then, non-pharmacological interventions, addressing residual inflammatory risk, such as vigorous physical activity, (intermittent) fasting and dietary carbohydrate restriction, all resulting in elevation of ketone body β-hydroxybutyrate (BHB), an endogenous inhibitor of the NLRP-3 inflammasome [30], should be strongly promoted in this very low risk population.

Finally, we also found that increased Cystatin C, hsTnI as well as NT-proBNP might be interesting indicators of increased CHD risk in individuals without CVRFs, providing an additional tool for better risk assessment in the absence of traditional risk factors. While those biomarkers might rather be an indication of already established but still asymptomatic diseases (e.g. CHD in case of cardiac biomarkers or preclinical kidney disease in case of Cystatin C [31,32]), their possible therapeutic lowering would not be consequential for ASCVD development.

4.1. Strengths and limitations of the study

The current study has several strengths. To our knowledge, the present analysis represents the first systematic investigation of various biomarker-related alternative pathways (metabolic, inflammatory, renal or cardiac-function related) to predict future CHD in individuals without five major risk factors at baseline. Centralized measurements of biomarkers using the same assays minimized analytical imprecision in measurements between individual BiomarCaRE cohorts. Finally, largely standardized baseline measurements and careful harmonization of the data from European population-based cohorts led to comparable and reliable data on risk factors and endpoint validation.

Our study also has several limitations which merit consideration. The present data cannot be extrapolated to other ethnic populations or age groups, since mainly middle-aged Caucasians were included in this analysis. Furthermore, we have no data on repeat measurements of biomarkers or covariates and hence, we were unable to follow the trajectory of risk or to take into account a regression dilution bias. More importantly, although per definition individuals have been considered to have no risk factors, they might still have a suboptimal risk factor profile (e.g., borderline arterial hypertension, borderline hypercholesterolemia) or even be underdiagnosed. In addition, not all possible mechanisms of CHD development in individuals without traditional CVRFs [20] could be evaluated in our analysis, since we have no data on dietary patterns and physical activity, as well as on thrombotic or environmental factors or inherited risk in those with zero risk factors. Finally, CHD assessment at baseline may have led to some misclassification, but we expect this to be small and non-differential across biomarker levels.

5. Conclusions

The results of the present analysis highlight the promising role of TGs or hsCRP for incident CHD beyond the five major modifiable CVRFs in the general population. Our study represents a first attempt to identify risk markers of future CHD events in those at very low absolute CV risk and thus to achieve a better understanding of non-traditional risk in this specific population. While biomarker-based risk stratification might improve CHD risk assessment in individuals without traditional CVRFs, the low absolute risk in this population necessitates a cautious interpretation of our findings. Therefore, from a public health perspective, a precise quantification of the risk is essential, as it may support a shift away from indiscriminate biomarker testing toward more focused, cost-effective prevention strategies.

Data availability statement

The data are not available in a public repository. Access to the data is restricted by the ethical approvals and the legislation of the European Union and the countries of each study. Approval by the Principal

Investigator of each cohort study and the MORGAM/BiomarCaRE Steering Group will be required for release of the data. The MORGAM Manual at https://www.thl.fi/publications/morgam/manual/contents.htm gives more information on access to the data.

CRediT authorship contribution statement

NA: study conceptualization, methodology, data curation, writing - original draft. AG: study conceptualization, data curation and statistical analyses, writing - review & editing. JW, FO: statistical analysis and consulting, writing – review & editing. BB; CW: data curation, methodology, writing – review & editing. TZ: laboratory analyses, data curation, writing - review & editing. MFF; LP; PA; MM; JF; HB; AT; SoMa; SaMä, WD; GG; SG: data collections (investigation, resources), writing – review & editing. AL; SSö LI; SS; RS; GV; BT; HTP; FK; VS; SB: study design, methodology, funding acquisition, writing - review & editing. KK: study design, project administration, funding acquisition, writing - review & editing. CM; WK: study conceptualization, supervision, writing – review & editing. All the authors approved the final article.

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Declaration of competing interest

Outside the scope of the present work, N.A. reports receiving lecture fees from Novartis, Sanofi and Amgen, consulting/advisory board fees and grant support from Novartis; travel support from Daiichi Sankyo; F. J.B. reports receiving grant supports from Daiichi Sankyo, Novartis, Pfizer, and Sanofi, non-financial support from Abbott, ASAHI INTECC and Inari Medical, personal fees from Amgen and Novartis; S. Sö. has received compensation for consultancy or speaking for Johnson & Johnson and Merck; R.S. reports personal fees from BMS/Pfizer; V.S. reports receiving grants from Bayer AG; S.B. reports receiving grants and personal fees from Abbott Diagnostics, Bayer, SIEMENS, Thermo Fisher, grants from Singulex, personal fees from Astra Zeneca, AMGEN, Medtronic, Pfizer, Roche, Siemens Diagnostic, Novartis; C.W. reports lecture fees from Astra-Zeneca; C.M. reports receiving speaker fees from Edwards, AstraZeneca, Novartis, Boehringer Ingelheim/Lilly, Bayer, and Novo Nordisk and consulting/advisory board fees from Boehringer Ingelheim and Novo Nordisk, W.K. reports receiving consulting fees and lecture fees from AstraZeneca, Novartis, and Amgen; consulting fees from Pfizer, The Medicines Company, DalCor Pharmaceuticals, Kowa, Corvidia Therapeutics, Esperion, Genentech, OMEICOS, Novo Nordisk, LIB Therapeutics, TenSixteen Bio, New Amsterdam Pharma and Daiichi Sankyo; lecture fees from Berlin-Chemie, Bristol-Myers Squibb, and Sanofi; and grant support and provision of reagents from Singulex, Abbott, Roche Diagnostics, and Dr Beckmann Pharma. All other authors declare no conflict of interest.

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Appendix A. Supplementary data

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