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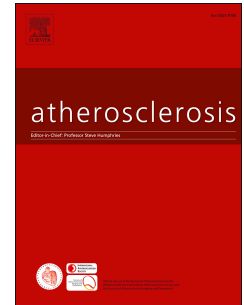
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1 **Association between plasma CD36 levels and incident risk of coronary heart disease**
2 **among Danish men and women**

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28 **ABSTRACT**

29 *Background and aims:* CD36 is a cholesterol receptor involved in the uptake of oxidized
30 low-density lipoprotein cholesterol and development of atherosclerotic plaques.

31 Cross-sectional studies have shown correlations between plasma CD36 and atherosclerosis
32 but no prospective study has examined the association yet. We prospectively examined the
33 association between plasma CD36 levels and risk of incident coronary heart disease (CHD) in
34 a Danish population.

35 *Methods:* Plasma CD36 levels were measured in a case-cohort study nested within the Danish
36 population-based cohort, the Diet, Cancer and Health Study. A total of 1,963 incident CHD
37 events occurred between baseline (1993-1997) and 2008, and a sub-cohort of 1,759
38 participants were randomly selected as reference. Cox proportional hazard regression models
39 were used to compute the hazard ratio (HR) and corresponding 95% confidence interval (CI).

40 *Results:* After adjusting for CHD risk factors, including history of hypercholesterolemia and
41 diabetes, elevated plasma CD36 levels were not associated with higher CHD risk in the total
42 population, and the HR comparing the highest *versus* lowest tertile of CD36 levels was 1.02
43 (95% CI 0.84-1.23). High CD36 levels were only found to be associated with risk of CHD in
44 combination with prevalent diabetes (HR=2.83, 95% CI: 1.08-7.45) *vs.* the joint reference
45 group of lowest CD36 tertile and no diabetes.

46 *Conclusions:* Plasma CD36 levels were not predictive of CHD risk in the general population.

47 **Keywords:** case-cohort study, coronary heart disease, plasma CD36, prospective study

48 **INTRODUCTION**

49 Coronary heart disease (CHD) arising from atherosclerosis is a leading cause of death
50 and morbidity worldwide [1]. Atherosclerosis is considered a chronic inflammatory disease
51 consists of plaque initiation, progression and thrombosis [2]. The transmembrane
52 glycoprotein CD36 is an important multi-ligand class B scavenger receptor in monocytes and
53 macrophages that internalizes oxidized low-density lipoprotein (ox-LDL) cholesterol in the
54 subendothelial spaces of arteries and subsequently differentiates the macrophages into foam
55 cells, which is the hallmark of early atherosclerotic lesions [3, 4]. In addition, CD36 is also a
56 fatty acid transporter in metabolically active tissues (muscle, liver and adipocytes) that is
57 implicated in the development of insulin resistance [5-7], which is another important risk
58 factor for developing atherosclerosis [8]. The importance of CD36 in the pathogenesis of
59 atherosclerosis has been shown in animal studies where double apoE/CD36 knockout mice
60 who develop significantly smaller atherosclerotic lesions compared to the wild-type controls
61 [9], have a doubling in lesion area when CD36 is reintroduced [10]. In addition, several
62 human genome-wide linkage studies have shown that the location of the *CD36* gene locus on
63 chromosome 7q is associated with myocardial infarction and stroke [11]. In addition, in
64 comparison to individuals with asymptomatic carotid plaques, CD36 gene expression has
65 been found to be up-regulated in patients with symptomatic carotid plaques [12]. This
66 suggests that CD36 could be a useful biomarker in the early development of cardiovascular
67 disease.

68 The expression of CD36 is increased in macrophages, smooth muscle cells, and
69 endothelial cells in atherosclerosis plaques [13]. However, previous studies of membrane
70 CD36 in monocytes and macrophages require fresh blood samples for measurement [14-17],
71 and thus were not well suited for large population-based epidemiological studies. To tackle
72 this issue, Handberg et al. [18] developed an assay to analyze the stored plasma samples, and

73 identified a circulating form of CD36 in human plasma. Plasma CD36 was hypothesized to
74 be released into the circulation as part of the low-grade inflammatory state in insulin
75 resistance and atherosclerosis [18], and the levels have been found to be moderately
76 correlated with membrane CD36 expression in liver tissue [19]. While two cross-sectional
77 studies have reported correlations between plasma CD36 and carotid atherosclerosis among
78 both healthy populations and patients with high-grade internal carotid stenosis [20, 21], one
79 study did not find such correlation among patients with early coronary artery disease [22].
80 Thus far, no prospective studies have been conducted to evaluate the association between
81 plasma CD36 and risk of CHD.

82 Therefore, we conducted a case-cohort study in a large population-based cohort
83 among Danish men and women to examine the association between plasma CD36 and risk of
84 CHD. We also investigated whether this association is modified by important cardiovascular
85 risk factors including obesity, smoking status, as well as history of hypercholesterolemia and
86 diabetes.

88 MATERIALS AND METHODS

89 *Study population*

90 The Danish Diet, Cancer and Health study is an ongoing prospective study established
91 between 1993 and 1997, and recruited 57,053 cancer-free participants aged between 50 and
92 65 years who lived in the urban areas of Copenhagen and Aarhus [23]. At baseline,
93 participants filled out self-administered lifestyle questionnaires, and the questions included
94 self-reported type 2 diabetes and hypercholesterolemia. In addition, technicians obtained
95 anthropometric measurements and collected non-fasting blood samples at the study clinic.
96 Blood specimens were separated into plasma, serum, lymphocytes, and erythrocytes and
97 frozen at -150°C within two hours of collection. The detailed design of the study has

98 described previously [23]. The study protocol complied with the Helsinki declaration and was
99 approved by the National Committee on Health Research Ethics and the Danish Data
100 Protection Agency (KF 01-116/96). Informed consent was completed and obtained from all
101 participants at the baseline interview.

102 CHD cases were identified via the National Diabetes Registry using the personal
103 identification number assigned to all Danish citizens in the Danish Civil Registration System.
104 Cases were identified when participants registered with a first-time discharge diagnosis of
105 myocardial infarction (International Classification of Diseases [ICD], 8th revision codes 410
106 to 410.99; and ICD 10th revision codes I21.0-I21.9) [24, 25]. Medical records were retrieved
107 from hospitals, reviewed in accordance with current guidelines [26], and myocardial
108 infarctions diagnoses in the National Diabetes Registry are recorded with a high degree of
109 validity [27]. Furthermore, we included participants with a sudden cardiac death diagnosis in
110 the Cause of Death Register (ICD 8: 427.27 or ICD 10: I46.0-I46.9) if the cardiac arrest after
111 validation was believed to be caused by a myocardial infarction.

112 We investigated the association between plasma CD36 and risk of CHD (non-fatal
113 myocardial infarction and fatal CHD) in a case-cohort study nested within the Danish Diet,
114 Cancer and Health study. For the current analysis, all confirmed incident cases between study
115 entry and May 2008 (n=1,977) were included along with a randomly chosen sub-cohort of
116 participants drawn from the entire study population at baseline (n=1,824). After additional
117 exclusion of participants with missing covariate values, the case-cohort included 1,963
118 incident CHD cases (58 within the reference sub-cohort) and 1,701 non-cases (sub-cohort
119 total n=1,759).

120 *Biochemical measurements*

121 For the measurement of CD36 concentrations, plasma samples from the baseline
122 exam were sent to Aarhus University hospital and Handberg's *in-house* ELISA assay was

123 used [18]. While phosphate-buffered saline was served as background, a pool of
124 ethylenediaminetetraacetic acid (EDTA) plasma was applied in increasing dilutions and used
125 to produce a standard concentration curve. Absorptions were calculated relative to the
126 standard EDTA plasma pool and expressed as relative units. Internal controls consisting of an
127 EDTA plasma pool and recombinant CD36 (generously donated by Randox, Laboratories
128 [Antrim, United Kingdom]) were run in duplicates and in four concentrations on each plate.
129 Analytical runs were accepted if one of the internal controls was within mean ± 1 standard
130 deviation (SD) and the other control was within ± 2 SD. The intra-assay coefficient of
131 variation (CV) was 11% (plasma pool, mean 0.14 arbitrary units), and total day-to-day assay
132 CV was 25% (plasma pool) and 19% (recombinant CD36). The relatively high CVs ($\geq 15\%$)
133 suggested the existence of moderate variability between batches. To account for batch
134 variability, we performed recalibration by regressing CD36 levels on batch and other
135 variables associated with CD36 levels including age, sex, smoking status, alcohol intake, and
136 education [28], that might have been unevenly distributed across batches by chance.

137 *Statistical methods*

138 We evaluated the baseline characteristics of participants who developed CHD during
139 follow-up and the random sub-cohort members separately with medians and 5th/95th
140 percentiles. The difference of plasma CD36 levels between gender, smoking status, adiposity
141 level, as well as history of diabetes and hypercholesterolemia were examined by two-tailed t
142 tests in sub-cohort population with adjustment for age and sex. Plasma levels of CD36 were
143 categorized into tertiles based on the distribution of CD36 in sub-cohort participants. Cox
144 proportional hazard regression using age as the underlying time-scale with standard inverse
145 probability weights and robust variation to account for the case-cohort design was used to
146 estimate the hazard ratio (HR) and corresponding 95% confidence interval (CI) of CHD
147 comparing the highest *versus* lowest tertile of plasma CD36 levels. Person-years were

148 calculated from the study entry to diagnosis of CHD, death, emigration, or end of follow-up
149 in 2008, whichever came first. Multivariable model was adjusted for potential confounders
150 including age (continuous), sex (men, women), smoking (never; former; current <15, 15-24,
151 ≥ 25 grams of tobacco/day), length of school education (short < 8; medium 8-10; long >10
152 years), BMI (continuous), alcohol intake (nondrinker; drinker, <5, 5-9, 10-19, 20-39, ≥ 40
153 grams of alcohol/day), as well as self-reported hypercholesterolemia and diabetes (yes, no).
154 In addition, we also examined the possible non-linear relation between plasma CD36 and
155 CHD risk using restricted cubic spline regression with 3 knots at 25th, 50th and 75th
156 percentiles of plasma CD36 concentrations. If no deviation from linearity was detected, we
157 also calculated the CHD risk associated with per SD increment of plasma CD36. Moreover,
158 age- and sex-adjusted means of plasma CD36 levels were compared between subgroups of
159 sex (men, women), smoking status (current smokers, non-smokers), history of diabetes (yes,
160 no), body mass index (<25 kg/m², 25-<30 kg/m², ≥ 30 kg/m²) and history of
161 hypercholesterolemia (yes, no). Furthermore, we evaluated the joint effect between tertiles of
162 plasma CD36 and different cardiovascular risk factors, using the lowest tertile of plasma
163 CD36 and the low-risk category of each risk factor as the reference. This corresponds to the
164 evaluation of biological interaction on the additive scale, as per Rothman. From these results,
165 we can qualitatively judge whether the combined exposure to high CD36 and a risk factor,
166 such as diabetes, is greater than expected based on the independent “effect” of each. To get a
167 *P* for interaction, we used the multiplicative model where plasma CD36 was modeled
168 continuously and included also the risk factor and interaction term between them. Data were
169 analyzed using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina). Two-sided *p*
170 values of <0.05 were considered to be statistically significant.

171

172

173 **RESULTS**174 *Population characteristics*

175 The characteristics of the case-cohort participants are shown in **Table 1**. The median
176 age at baseline was 58 years for the participants that developed CHD and 55 years for the
177 randomly selected sub-cohort individuals. In comparison to the sub-cohort participants, those
178 who developed CHD were more likely to be male, current smokers, had higher BMI, lower
179 education, and history of diagnosed hypercholesterolemia or diabetes. In addition, cases had
180 higher concentrations of plasma CD36 compared with sub-cohort participants. Within the
181 sub-cohort, the mean value of plasma CD36 levels was substantially higher among men
182 compared to women ($p=0.04$; **Table 2**), and among obese participants compared to subjects
183 with normal weight ($p=0.02$; **Table 2**).

184 *Associations of plasma CD36 and CHD risk*

185 After adjustment for age, sex and lifestyle factors, elevated plasma CD36 levels were
186 not associated with higher risk of CHD; the HR comparing the highest *versus* lowest tertile of
187 plasma CD36 levels was 1.02 (95% CI 0.84- 1.23; **Table 3**). Restricted cubic spline
188 regression analysis did not suggest a non-linear relationship between plasma CD36 and CHD
189 risk ($p=0.99$ for nonlinearity; **Supplementary Figure 1**). When modelling plasma CD36 as a
190 continuous variable, the HR (95% CI) for CHD with per-1 SD increment in plasma CD36
191 was 1.01 (0.93-1.07) in the multivariable model. The results were materially unchanged after
192 further adjustment for postmenopausal status and hormone therapy. In sensitivity analyses,
193 we repeated the analysis after trimming CD36 levels by 5th and 95th percentile, and found a
194 similar association between plasma CD36 and CHD risk (HR per SD:1.05; 95% CI
195 0.92-1.19).

196 *Joint analysis with cardiovascular risk factors*

197 In joint models, a higher CD36 level did not add to the risk of CHD beyond sex,

198 smoking, obesity, and hypercholesterolemia (**Table 4**). However, elevated plasma CD36
199 levels were associated with higher CHD-risk among people with diabetes. Compared with
200 participants who were in the lowest plasma CD36 tertile and free of diabetes, higher CD36
201 levels were not associated with higher CHD-risk among non-diabetic individuals (HR
202 comparing the highest *versus* lowest tertile of plasma CD36 levels was 1.00 (95% CI 0.83-
203 1.21), whereas the HR among participants was 2.83 (95% CI: 1.08, 7.45) for diabetic
204 participants with the highest CD36 level. Nevertheless, no significant interactions were
205 observed between CD36 with all these cardiovascular risk factors (all *P*-interaction >0.05).

206

207 **DISCUSSION**

208 In this large, prospective case-cohort study among Danish men and women, elevated
209 plasma CD36 levels were not associated with higher CHD-risk in the overall population.
210 However, a suggestive positive association between elevated plasma CD36 levels and higher
211 CHD-risk was observed among participants with prevalent diabetes.

212 Thus far, only cross-sectional studies have been conducted to explore the relationship
213 between plasma CD36 and presence of atherosclerosis [20-22]. Among 62 Norwegian
214 patients with high-grade internal carotid stenosis, Handberg et al. [21] found that patients
215 with echolucent carotid plaques had higher plasma CD36 than those with
216 echogenic/heterogeneous plaques, and suggested that CD36 may play a critical role in plaque
217 instability and symptomatic carotid atherosclerosis. Furthermore, a study of 1029 healthy
218 individuals from 14 European countries found a weak correlation ($r=0.10$; $p<0.01$) between
219 plasma CD36 and carotid atherosclerosis as reflected by intima-media thickness [20].
220 However, in contrast, a recent study from Poland did not find any significant correlations
221 between plasma CD36 concentrations and atherosclerosis (using a comprehensive set of
222 radiological parameters) among 70 patients with early-onset coronary artery disease [22].

223 Reverse causality is a concern in these reports since the temporal relations cannot be
224 determined from cross-sectional studies. To the best of our best knowledge, the current study
225 is the first prospective population-based study to investigate the association between plasma
226 CD36 and CHD-risk. During the 14-year follow-up, we did not observe a positive association
227 between plasma CD36 levels and CHD risk in the general population, but we found a
228 moderate positive association among participants with self-reported diabetes. However, given
229 the multiple statistical tests and small number of diagnosed diabetes cases, our observed
230 association between plasma CD36 and CHD among participants with prevalent diabetes
231 could also be due to chance, and should be interpreted with caution.

232 Although the underlying mechanism is not clear yet, plasma CD36 was previously
233 hypothesized to be released into the circulation as part of the low-grade inflammatory state in
234 insulin resistance and atherosclerosis in a previous study [18]. Plasma CD36 levels
235 moderately correlated with membrane CD36 expression in liver tissue (correlation=0.37;
236 $p=0.07$) [19], and elevated plasma CD36 levels were observed in obese people and patients
237 with type 2 diabetes, in accordance with raised tissue CD36 expression reported by others [5,
238 15, 16, 29, 30].

239 Several lines of experimental evidence also suggests that membrane CD36 is
240 implicated in the pathophysiology of developing insulin resistance and atherosclerosis
241 [31-33]. In the presence of high glucose levels or insulin resistance, membrane CD36
242 transcription and expression is upregulated and could lead to an almost 10-fold increase in
243 CD36 mediated ox-LDL uptake [15, 29, 34], and thus may provide a mechanism for
244 accelerated atherosclerosis in diabetic patients [29]. In addition, ox-LDL uptake by CD36 has
245 shown to be dependent on the fatty acid that simultaneously binds to the same receptor [35].
246 Interestingly, recent studies have demonstrated that medications (peroxisome
247 proliferator-activated receptor-gamma agonist and metformin), exercise and food extracts

248 (green tea polyphenols and cinnamon) could decrease CD36 expression in animal models and
249 plasma levels in humans [34, 36-39]. Future studies should investigate whether such
250 interventions might lower plasma CD36 among people with type 2 diabetes, and if lowering
251 the plasma CD36 level translates into decreasing CHD-risk

252 Given the previous associations particularly with echolucent plaques, we propose that it
253 would be worthwhile to expand the endpoint from pure CHD to all cardiovascular disease
254 (such as including stroke events). Our current study only included CHD events and we cannot
255 exclude that associations with stroke might be stronger.

256 Our study has the strength of assessing the association between plasma CD36 and
257 CHD risk, as well as exploring potential interactions with other CVD risk factors. In addition,
258 the present study is a prospective design with large sample size; hence the recall bias in the
259 exposure data prior to CHD diagnosis does not exist. However, some limitations merit
260 consideration. First, we were only able to investigate the risk of CHD as we did not have
261 plasma samples from stroke cases. Moreover, type 2 diabetes cases were self-reported in the
262 current study and not identified by standardized blood testing, thus, underestimation of the
263 type 2 diabetes may exist. In addition, we included relatively small number of diabetes cases
264 and thus may have limited statistical power for the stratified analyses, however, our direction
265 of association pointed towards the same direction compared to previous observations [18, 40,
266 41]. Furthermore, we observed moderate batch variability, which was accounted for by
267 batch-recalibration. However, even though this methodology can break any potential
268 association between CD36 and potential confounders in the final Cox models, a smaller CV
269 for the CD36 measurement would provide greater statistical power and precision in our
270 analysis. As such, we cannot exclude that the largely null result in our study could be partly
271 explained by our measurement error. Additionally, the present study was conducted among a
272 Caucasian population living in Northern Europe, and the results may not be applicable to

273 other ethnic groups.

274

275 *Conclusions*

276 In conclusion, we have observed that elevated plasma CD36 levels not associated
277 with higher CHD risk in a general population. A tendency for a higher risk was observed
278 among participants with diabetes. Plasma (or circulating) CD36 concentration could be an
279 interesting new marker that may link diabetes and atherosclerosis but future longitudinal
280 studies are needed to examine the role of CD36 and risk of cardiovascular disease,
281 particularly stroke, and to validate our findings in other ethnic groups.

282

283 **Conflict of interest**

284 Dr. Handberg and the Ideas Clinic at Aalborg University Hospital hold two patents for the
285 measurement of CD36 in plasma: "Method of evaluation of the relative risk of developing
286 atherosclerosis in patients" 2006, WO2005/116644 and "A method for diagnosing
287 atherosclerotic plaques by measurement of CD36", 2008, WO2008/ 095492.

288

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291 samples. The Diet, Cancer and Health Study was funded by the Danish Cancer Society.

292

293 **Author contributions**

294 MKJ conceived the study, interpreted the data, and critically revised the reports. JZ analyzed
295 and interpreted the data, and drafted the reports. YW drafted and critically revised the reports.
296 AH measured the plasma samples of CD36 and critical revised the reports. KO, AT and EBR
297 critically revised the reports.

298

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Table 1. Characteristics of participants who developed CHD during follow-up and sub-cohort members in the Diet, Cancer and Health study

Variable	Sub-cohort	CHD cases
N	1759	1963
Age (yrs)	55.0 (50.0, 64.0)	58.0 (51.0, 64.0)
Women	46.5%	27.2%
Postmenopausal (women) ^a	58.3%	71.0%
Current estrogen use ^a	31.7%	29.0%
Education < 8 yrs, % (N)	33.5%	45.0%
Current smoker, % (N)	37.8%	54.8%
Alcohol, g/d	13.6 (0.7, 65.7)	13.6 (0.2, 69.2)
Physical activity, METs/wk	60.00 (19.5, 155.0)	58.5 (16.5, 163.8)
BMI (kg/m ²)	25.6 (20.5, 33.0)	26.7 (21.1, 34.7)
Diabetes ^b	1.8%	5.5%
Hypertension ^b	18.4%	31.3%
Hypercholesterolemia ^b	8.0%	13.0%
Plasma CD36, arbitrary units	0.62 (0.08, 2.67)	0.65 (0.08, 2.57)

Median (5th and 95th percentiles) or %.

^aAmong women.

^bSelf-reported physician-diagnoses of diabetes, hypertension, and hypercholesterolemia.

Table 2. Least-squares means of plasma CD36 level in randomly selected participants from the Danish Diet, Cancer and Health Study.

	Mean CD36 level (95% CI)	<i>p</i> ^a
Men	0.91 (0.85, 0.96)	
Women	0.82 (0.76, 0.88)	0.04
Non smokers	0.90 (0.84, 0.95)	
Current smokers	0.81 (0.75, 0.88)	0.07
Non-diabetes	0.87 (0.83, 0.91)	
Diabetes	0.71 (0.40, 1.03)	0.33
Normal weight	0.82 (0.75, 0.88)	
Overweight	0.88 (0.82, 0.94)	0.18
Obesity	0.97 (0.86, 1.08)	0.02
Non hypercholesterolemia	0.86 (0.81, 0.90)	
Hypercholesterolemia	0.97 (0.82, 1.12)	0.16

Data were means (95% CI), adjusted for age and sex (where appropriate).

^a*p* values for test of difference in means of CD36.

Table 3. Hazard Ratios (HRs) and 95% confidence intervals (95% CI) for coronary heart disease risk according to plasma CD36 level.

	Tertiles of plasma CD36			Continuous	
	T1	T2	T3	Per SD (0.87 unit)	<i>p</i>
N cases/N at sub-cohort	595/586	676/588	692/585		
Median (interquartile range)	0.24 (0.12-0.33)	0.62 (0.52-0.73)	1.32 (1.03-2.04)		
Age and sex adjusted HR (95% CI)	1 (ref)	1.03 (0.87, 1.23)	1.03 (0.87, 1.22)	1.00 (0.93, 1.07)	0.89
Multivariable model HR ^a (95% CI)	1 (ref)	1.00 (0.83, 1.21)	1.02 (0.84, 1.23)	1.01 (0.94, 1.09)	0.71

HRs were obtained from Cox proportional hazard regression models stratified by sex.

Tertiles created based on the distribution in the random sub-cohort. *p*-values were calculated using the continuous CD36 variables.

^aMultivariable model: adjusted for age, sex, BMI, smoking, alcohol, physical activity, education, self-reported hypercholesterolemia, and diabetes.

Table 4. Hazard ratios (HRs) and 95% confidence intervals for risk of coronary heart disease by joint categorization of CD36 tertiles and cardiovascular disease risk factors and continuous CD36 within strata.

	Tertiles of plasma CD36			Continuous	
	T1	T2	T3	Per SD (0.87 unit)	<i>p</i>
Gender					
Female (N=1,336/N cases=534)	1 (ref)	1.08 (0.81, 1.43)	1.02 (0.76, 1.36)	0.98 (0.86, 1.13)	0.8
Male (N=2,328/N cases=1,429)	2.76 (2.10, 3.64)	2.68 (2.07, 3.48)	2.80 (2.16, 3.62)	1.03 (0.94, 1.13)	0.5
Current smoking status					
No smoking (N=1,961/N cases=888)	1 (ref)	1.01 (0.79, 1.28)	0.96 (0.76, 1.22)	0.99 (0.90, 1.09)	0.8
Current smoking (N=1,703/N cases=1,075)	2.01 (1.54, 2.63)	2.02 (1.57, 2.60)	2.16 (1.66, 2.80)	1.04 (0.93, 1.16)	0.5
Normal/Overweight/Obesity					
BMI <25 kg/m ² (N=1,362/N cases=603)	1 (ref)	1.15 (0.86, 1.55)	1.08 (0.80, 1.47)	1.03 (0.90, 1.18)	0.6
BMI 25-30 kg/m ² (N=1,638/N cases=923)	1.51 (1.13, 2.02)	1.47 (1.11, 1.95)	1.59 (1.19, 2.11)	1.01 (0.91, 1.11)	0.9
BMI ≥30 kg/m ² (N=664/N cases=437)	2.71 (1.71, 4.30)	2.09 (1.45, 3.00)	1.97 (1.38, 2.82)	0.96 (0.79, 1.18)	0.7
Diabetes					
No diabetes (N=3,530/N cases=1,855)	1 (ref)	1.00 (0.83, 1.21)	1.00 (0.83, 1.21)	1.01 (0.93, 1.08)	0.9
Diabetes (N=134/N cases=108)	2.11 (0.87, 5.13)	1.99 (0.99, 3.99)	2.83 (1.08, 7.45)	1.37 (0.92, 2.04)	0.1
Hypercholesterolemia					
No hypercholesterolemia (N=3,281 /N cases=1,707)	1 (ref)	1.06 (0.87, 1.30)	1.09 (0.89, 1.33)	1.01 (0.94, 1.09)	0.8
Hypercholesterolemia (N=383/N cases=256)	2.41 (1.45, 3.98)	1.48 (0.96, 2.27)	1.49 (0.98, 2.26)	1.06 (0.80, 1.42)	0.7

Models were adjusted for age, alcohol, physical activity, education; and for sex, smoking, BMI, self-reported hypercholesterolemia, and diabetes where appropriate.

- CD36 was not associated risk of coronary heart disease in the total population.
- There was a suggestion of higher risk of coronary heart disease among participants with both high CD36 levels and existing diabetes.

ACCEPTED MANUSCRIPT