

REVIEW ARTICLE

Carotid intima-media thickness and markers of inflammation, endothelial damage and hemostasis

DAMIANO BALDASSARRE^{1,2}, ARIENNE DE JONG¹, MAURO AMATO², J. PABLO WERBA², SAMUELA CASTELNUOVO¹, BEATRICE FRIGERIO¹, FABRIZIO VEGLIA², ELENA TREMOLI^{1,2} & CESARE R. SIRTORI¹

¹E. Grossi Paoletti Center, Department of Pharmacological Sciences, University of Milan, Italy, and ²Cardiologico 'Monzino' Center, IRCCS, Milan

Abstract

Background. Different soluble molecules involved in inflammation, endothelial damage, or hemostasis are recognized as potential cardiovascular risk markers. Studies to assess the role of these markers in the atherosclerotic process by evaluating their relationship to carotid intima-media thickness (C-IMT) tend to provide contrasting results.

Purpose. To perform a review of studies addressing the association between C-IMT and soluble markers and to investigate whether the observed inconsistencies could be explained by the characteristics of the patients included in different studies, for example prevalence of atherosclerotic disease (atherosclerotic burden), gender, age, or occurrence of specific vascular risk factors (VRFs).

Data sources. PubMed and Embase (January 1990 to March 2006).

Study selection. Articles in English reporting original cross-sectional studies.

Data extraction. Two authors independently extracted data on study design, population, sample size, ultrasonic methodology, and statistical approach.

Data synthesis. Despite the marked heterogeneity of results presented in the literature, meta-analysis established that studies showing positive associations between C-IMT and plasma levels of C-reactive protein (CRP) or fibrinogen are in the majority. Funnel plot analyses suggested the absence of an important publication bias. Data on the relationships between C-IMT and other soluble markers are by contrast scanty, contradictory, or unconfirmed by multivariate (as opposed to univariate) analyses, and the freedom from publication bias here cannot be vouched for. The degree of atherosclerotic burden in the population studied does not account for the heterogeneity of findings reported. Gender, noninsulin-dependent diabetes mellitus (NIDDM) and hypercholesterolemia influence the association between C-IMT and CRP. Blood pressure and hypercholesterolemia influence the association between C-IMT and fibrinogen. For all the other soluble markers considered, the number of groups was too small for this kind of statistical considerations.

Limitations. Heterogeneity in ultrasound methodologies and in statistical approach limited comparability between studies. For most soluble markers, publication bias of positive results cannot be excluded.

Conclusions. Only CRP and fibrinogen seem to be unequivocally related to C-IMT. For all the other soluble markers considered, no clear-cut conclusions can be drawn.

Key words: Atherosclerosis, carotid ultrasound, endothelial damage, hemostasis, imaging, inflammation

Introduction

A number of soluble markers of inflammation, endothelial damage and hemostasis have been linked with the atherosclerotic process (1). On the basis of the relationship of their plasma levels with the occurrence/extent of atherosclerosis, these molecules have been evaluated as predictors of cardiovascular

events, as promoters of disease progression, and as determinants of the effectiveness of cardiovascular therapies (2). These associations could arise from the involvement of these soluble markers in basic phenomena of the atherogenic process. Activated monocytes adhere to the endothelium through intercellular and vascular adhesion molecules (ICAM and VCAM) and migrate through the

Abbreviations

Bif	bifurcation
BMI	body mass index
CAD	coronary artery disease
CC	common carotid
C-IMT	carotid intima-media thickness
CRP	C-reactive protein
CVD	cardiovascular disease
FH	familial hypercholesterolemia
ICA	internal carotid artery
ICAM	intercellular adhesion molecule
IL	interleukin
LDL-C	low-density lipoprotein cholesterol
MCP-1	monocyte chemoattractant protein-1
MMP	matrix metalloproteinases
NIDDM	noninsulin-dependent diabetes mellitus
PAI-1	plasminogen activator inhibitor-1
SAA	serum amyloid A
TFPI	tissue factor pathway inhibitor
TIMP	tissue inhibitors of metalloproteinases
TNF α	tumor necrosis factor α
t-PA	tissue plasminogen activator
VCAM	vascular cell adhesion molecule
VRFs	vascular risk factors

endothelial layer, a process facilitated by E-selectin and monocyte chemoattractant protein-1 (MCP-1). In the subendothelial space, monocytes differentiate into macrophages, subsequently filled with modified cholesterol-rich lipoproteins to become foam cells. This process is amplified by cytokines and acute phase reactants and leads to fatty streak development, the first step in atherosclerotic plaque formation. Increased platelet adherence/aggregation plays an important role in this process (3).

Besides the association of soluble markers with angiographic measures of atherosclerosis or with clinical vascular events, their role in the atherosclerotic process may be estimated by investigating their relationship with subclinical atherosclerosis assessed by noninvasive techniques. One of most favored markers of atherosclerosis is the thickness of the intima-media complex in carotid arteries, the IMT (4). On the basis of 20 years of research, carotid IMT (C-IMT) is now widely accepted as a surrogate marker of carotid/coronary atherosclerosis and a predictor of cardiovascular events (5–7).

Key messages

- C-reactive protein and fibrinogen are the soluble markers most frequently related significantly to subclinical atherosclerosis as measured by carotid intima-media thickness (C-IMT).
- The atherosclerotic burden of the groups investigated does not account for the heterogeneity of reported findings relating to associations between soluble markers and C-IMT.
- Studies using highly standardized protocols for C-IMT measurement and rigorous multivariate statistical approaches are needed to elucidate the still controversial relationship between soluble markers and C-IMT.

Carotid IMT increases naturally with aging (8), but conventional and nonconventional atherosclerosis risk factors may accelerate the process (9). More than a hundred studies have been published so far associating C-IMT and these soluble markers, but opposing data have also been reported.

The present review summarizes these findings and investigates whether the dissimilar prevalence of atherosclerotic disease (atherosclerotic burden) in patients included in the different studies could explain the observed inconsistencies. For this purpose, data from studies in groups with increasingly higher atherosclerotic burdens were compared. The literature was further explored to search for other potential characteristics of patients that might influence the C-IMT-soluble markers associations.

Methods

PubMed and Embase from 1990 to March 2006 were searched for articles in English, using the following keywords: IMT OR intima media thickness OR intimal medial thickness AND the full name or abbreviations of all soluble markers listed in Table I, one at a time. Synonyms of soluble markers were identified in the iHOP web page and included in the literature search.

Only cross-sectional studies examining the relationship between C-IMT and soluble markers of low-grade inflammation, endothelial damage, and hemostasis were included. References of included articles were also examined for relevant studies.

Articles considered of low methodological quality were excluded. The key criteria of quality were:

reproducibility of ultrasound method, appropriateness of control group, and clarity of definition of inclusion and exclusion criteria.

Methods and results of all studies selected were tabulated. Data from studies reporting univariate or multivariate correlation/associations were included in the analyses.

A Fisher's exact test was first performed to assess whether the number of significant results among the published studies was different from expected according to the null hypothesis of no correlation between each soluble marker and C-IMT. Moreover, a funnel plot was used to evaluate publication bias (10). For this analysis the correlation coefficients were normalized (i.e. transformed in order to obtain a variable with a normal distribution) according to the formula of Fisher (11).

In order to assess whether the atherosclerotic profile of the population studied affects the association between C-IMT and soluble markers, the results from studies performed in healthy subjects, general populations, patients with vascular risk factors (VRFs) (e.g. hyperlipidemia, hypertension, or type 2 diabetes), and patients with overt atherosclerotic cardiovascular disease (CVD) were compared, assuming that the disease prevalence, herein termed 'atherosclerosis burden', progressively increase from the first to the last group.

Age, gender, and the prevalence of dyslipidemia, obesity, diabetes mellitus, or hypertension in the different studies were considered as further potential sources of inconsistency in the reported results.

Results

The search strategy identified 370 articles; 136 were rejected after reading the title and abstract, because they: 1) included patients with acute or chronic inflammatory diseases (e.g. rheumatoid arthritis) or inflammatory conditions (e.g. chronic renal failure), 2) included only children, 3) reported only relationships with genotypes, 4) were *ex vivo* studies, 5) were reviews, 6) were intervention studies not reporting baseline data, 7) described protocols of studies not yet performed, or 8) were published after March 2006 unless e-publication was available before this date.

Among the 239 full articles retrieved, 131 were rejected because they: 1) were longitudinal studies not reporting baseline data, 2) were studies performed only after meals, 3) did not report correlations or associations between C-IMT and soluble markers, 4) assessed atherosclerosis in arteries other than carotids or used ultrasonic measurements other than IMT, 5) did not clearly describe the patient

recruitment method, 6) did not provide data on ultrasound reproducibility, 7) did not discuss the valid comparability of groups or did not describe inclusion or exclusion criteria clearly, and 8) did not determine C-reactive protein (CRP) by a highly sensitive method.

A total of 107 articles were finally considered for this review, including one progression study (12) which also reported baseline cross-sectional data. Table I summarizes the characteristics of the patient groups included in the studies herein reviewed.

Markers of low-grade inflammation

C-reactive protein

C-reactive protein (CRP) is an acute phase protein that is synthesized by the liver during inflammation in response to interleukin (IL)-6 and other proinflammatory cytokines as well as by vascular smooth muscle cells (13,14). An active role of this protein in atherogenesis has been suggested (15). The plasma concentration of CRP is also considered an independent predictor of the incidence and progression of cardiovascular disease (CVD) that is even more powerful than conventional VRFs such as low-density lipoprotein cholesterol (LDL-C) (16).

The relationship between plasma levels of CRP and C-IMT was investigated in 65 groups within 54 studies (17–70). A significant univariate correlation/association was found in 39 groups (60%) within 29 studies (19,23,25,27,32,33,35,37–40,42,44–46,48,49,52,55,57–60,62,66–70), whereas fewer than 4 (5%) were expected by chance if there were no relationship between the two variables ($P < 0.001$ by Fisher's exact test) and assuming no publication bias.

Figure 1 shows the funnel plot analysis of univariate correlations between plasma levels of CRP and C-IMT obtained by plotting correlation coefficients versus the sample size of the groups. The overall result (dashed line in the figure) supports a significant positive correlation between C-IMT and CRP concentrations. Although the distribution is not perfectly symmetrical, the absence of publication bias is suggested by the lack of change in the overall effect after studies with fewer than 100 or even 200 patients (data not shown) are excluded.

The number of groups with significant univariate associations was significantly higher than expected in population-based cohorts (19 out of 20; versus 1 expected by chance alone, $P < 0.0001$ by Fisher's exact test) (32,33,35,37–40,42,44–46,48) and in groups of patients with VRFs (11 out of 28; versus 1.4, $P < 0.0001$) (23,26,30,32–37). Although in

Table I. Characteristics of studies reviewed.

Progressive number of articles reviewed	First author, year of publication (reference)	Subjects ^a	n (male %)	Age (mean)	Location ^b	IMT (mm) ^c	Univariate correlation or association	Multivariate correlation or association
Highly sensitive determination of C-reactive protein (hs-CRP):								
1	Hak 1999 (29)	Healthy (w never-smokers)	99 (0)	51	CC R (F+N)	n.r.	n.p.	No
2	Holmlund 2002 (80)	Healthy	59 (54)	50	CC (F)	0.76	No	n.p.
3	Hulthe 2002 (38)	Healthy	365 (100)	58	CC/Bif/ICA (Comp) (F)	0.8	Yes	No
4	Halenka 2004 (24)	Healthy	40 (46)	39	CC (plaque excl.) (F)	0.6	No	No
5	Leinonen 2004 (53)	Healthy	78 (62)	61	Max IMT	1.05	No	n.r.
6	Moussavi 2004 (49)	Healthy	25 (58)	54	CC (F)	0.63	No	No
7	Saijo 2004 (39)	Healthy	113 (43)	36	CC (F)	0.53	Yes	No
8	Sigurdardottir 2004 (148)	Healthy	197 (100)	61	CC/Bif and (CC+Bif) (F)	0.77	No	n.p.
9	Beloqui 2005 (40)	Healthy	291 (77)	58	CC (plaque excl.) (F+N)	0.71	Yes	No
10	Bowden 2005 (50)	Healthy	115 (41)	61	CC (F+N)	0.7	No	No
11	Choi 2005 (41)	Healthy	820 (53)	52	MM CC (F)	0.73	Yes	No
12	de Vries 2006 (51)	Healthy	83 (58)	57	CC/Bif/ICA R (F)	0.814	n.p.	No
13	Lo 2006 (52)	Healthy	100 (0)	40	CC L (F)	0.61	No	No
14	Folsom 2001 (149)	Popul (m and w)	875 (100) and 948 (0)	54	CC/Bif/ICA (F)	n.r.	n.p.	No
15	Markus 2001 (42)	Popul	291 (100)	62	MeanCC and MaxCC (F)	n.r.	n.p.	Yes
16	Sitzer 2002 (43)	Popul	1018 (50)	54	CC (F)	n.r.	Yes	Yes
17	van der Meer 2002 (44)	Popul	1317 (46)	67	CC (F+N)	n.r.	Yes	Yes
18	Wang 2002 (102)	Popul	3173 (48)	47	MM CC/Bif/ICA (F+N)	n.r.	n.p.	No
19	Cao 2003 (150)	Popul (controls and total group)	4948 (41.4) and 5417 (41.4)	73	MM CC/ICA (F+N)	1.05 and 1.09	No in controls, Yes in the total group	n.p.
20	de Maat 2003 (45)	Popul	695 (47)	60	CC/Bif R (F+N)	0.72	n.p.	Yes
21	Karvonen 2003 (151)	Popul	1022 (50)	51	MeanCC and MaxCC/Bif/ICA	0.88	Yes	No
22	Muscari 2003 (126)	Popul	288 (100)	59	MaxBif (F)	2.29	Yes	No
23	Amar 2004 (84)	Popul	891 (53)	49	CC (plaque excl.) R (F)	0.59	Yes	n.p.
24	Chapman 2004 (66)	Popul	1111 (50)	53	CC (plaque excl.) (F)	n.r.	Yes	No
25	Devynck 2004 (46)	Popul	84 (100)	48	CC (F)	0.58	n.r.	Yes
26	McDonald 2004 (47)	Popul	218 (44)	37	CC	0.63	Yes	Yes
27	Elkind 2005 (62)	Popul	141 (42)	67	MM CC/Bif/ICA (F+N)	0.89	No	n.p.
28	Makita 2005 (143)	Popul (m and w)	1290 (63) and 766 (63)	58	MaxCC (plaque excl.) (F)	n.r.	Yes	No
29	Mitusch 2005 (127)	Popul	1032 (52)	n.r.	MeanCC and MaxCC	0.84	Yes	n.p.
30	Yamagami 2005 (68)	Popul	366 (49)	65	MM CC/Bif/ICA (F+N)	0.99	Yes	No
31	Ahluwalia 2006 (82)	Popul	896 (53)	n.r.	CC (plaque excl.) (F)	0.59	n.r.	No

Table I. (Continued)

Progressive number of articles reviewed	First author, year of publication (reference)	Subjects ^a	n (male %)	Age (mean)	Location ^b	IMT (mm) ^c	Univariate correlation or association	Multivariate correlation or association
32	Ashfaq 2006 (152)	Popul	114 (41)	44	CC (F+N)	n.r.	Yes	No
33	Blackburn 2001 (23)	Lipid	1051 (62)	51	CC (plaque excl.)	0.64	Yes	No
4	Halenka 2004 (24)	Lipid	82 (46)	39	CC (plaque excl.) (F)	0.7	No	No
34	Sebestjen 2005 (25)	Lipid	72 (100)	46	MM CC/Bif/ICA (F)	0.86	No	n.p.
35	Choi 2004 (20)	Hypertens	122 (37)	48	CC R	0.65	No	No
36	Takiuchi 2004 (26)	Hypertens	184 (52)	64	MeanCC, MaxCC and MM CC	0.81	Yes	n.p.
37	Manabe 2005 (27)	Hypertens	41 (49)	62	CC (plaque excl.) (F)	0.81	No	No
38	Zavaroni 2006 (28)	Hypertens	63 (49)	55	CC (F)	0.96	No	n.p.
35	Choi 2004 (20)	Hypertens+healthy	186 (37)	48	CC R	0.62	No	No
39	Balletshofer 2005 (30)	NIDDM risk	81 (44)	33	CC (F)	0.5	Yes	Yes
40	Ahmad 2006 (31)	NIDDM risk (with and without)	38 (78)	30	CC/Bif and (CC+Bif)	0.51 and 0.47	No	n.p.
41	Festa 2001 (32)	NIDDM and at risk (m, w and m+w)	652 (100), 801 (0) and 1453 (45)	55	CC and ICA	CC in m and w: 0.852 and 0.794, respectively). ICA in m and w: 0.925 and 0.835 m+w= CC=0.82. ICA=0.88	CC: Yes in m, No in w, Yes in m+w. ICA: No in m, Yes in w, No in m+w	CC: Yes in m, No in w, Yes in m+w. ICA: No in m, Yes in w, No in m+w
42	Esposito 2004 (33)	NIDDM	401 (60)	56	CC	0.87	Yes	Yes
43	Kang 2004 (34)	NIDDM	105 (56)	55	Mean and Max IMT	0.63	Yes	n.p.
5	Leinonen 2004 (53)	NIDDM	239 (62)	61	Max IMT	1.19	No	n.r.
6	Moussavi 2004 (49)	NIDDM	40 (58)	54	CC (F)	0.63	No	No
8	Sigurdardottir 2004 (148)	NIDDM	74 (100)	61	CC/Bif and (CC+Bif) (F)	0.86	No	No
44	Takebayashi 2004 (35)	NIDDM	18 (39)	58	CC R	1.06	Yes	No
45	Berneis 2005 (54)	NIDDM (with and without CHD+total group)	9 (52) and 29 (52) and 38 (65.8)	61	CC (F)	1.05 and 0.88 and 0.96	n.p., n.p., No	No
10	Bowden 2005 (50)	NIDDM	551 (41)	61	CC (F+N)	0.65	No	No
46	Tajiri 2005 (36)	NIDDM	295 (55)	60	CC (F)	0.7	Yes	Yes
12	de Vries 2006 (51)	NIDDM	87 (58)	57	CC/Bif/ICA R (F)	0.876	n.p.	No
47	Takebayashi 2006 (116)	NIDDM	70 (47)	60	CC R	n.r.	No	n.p.
48	Kang 2005 (37)	NIDDM with/without MS	269 (57)	55	MeanCC and MaxCC (plaque excl.)	0.595 and 0.77	Yes	Yes
1	Hak 1999 (29)	W ever-smokers	87 (0)	51	CC R (F+N)	n.r.	No	Yes
19	Cao 2003 (150)	Overt-CVD	469 (42.4)	74.2	MM CC/ICA (F+N)	1.12	No	n.p.
49	Winbeck 2002 (48)	Overt-CVD	411 (52)	64	CC (F)	0.985	n.p.	Yes
50	Arroyo-Espliguero 2003 (17)	Overt-CVD (syndrome X)	30 (17)	57	CC (F)	0.75	Yes	n.r.

Table I. (Continued)

Progressive number of articles reviewed	First author, year of publication (reference)	Subjects ^a	n (male %)	Age (mean)	Location ^b	IMT (mm) ^c	Univariate correlation or association	Multivariate correlation or association
51	Orem 2003 (18)	Overt-CVD	64 (88)	58	CC (plaque excl.) (F)	0.82	Yes	n.p.
52	Benbir 2005 (19)	Overt-CVD	104 (n.r.)	n.r.	MM CC (plaque excl.) (F+N)	n.r.	Yes	n.p.
53	Magyar 2003 (21)	Overt-CVD+healthy	100 (58)	48	CC (F)	0.9	Yes	n.r.
54	Kojima 2005 (22)	Overt-CVD+healthy	250 (66)	68	Max IMT	n.r.	Yes	n.p.
Tumor necrosis factor α (TNF α):								
3	Hulthe 2002 (38)	Healthy	365 (100)	58	CC/Bif/ICA (Comp) (F)	0.8	No	n.p.
55	Skoog 2002 (57)	Healthy	96 (100)	50	CC (F+N)	0.86	Yes	No
56	Elkind 2002 (58)	Popul	245 (49)	68	Max Bif/ICA	0.82	No	No
27	Elkind 2005 (62)	Popul	141 (42)	67	MM CC/Bif/ICA (F+N)	0.89	No	n.p.
34	Sebestjen 2005 (25)	Lipid	72 (100)	46	Max CC/Bif/ICA (F)	0.86	No	n.p.
40	Ahmad 2006 (31)	NIDDM risk (with and without)	38 (78)	30	CC/Bif and (CC+Bif)	0.51 and 0.47	No	n.p.
57	Matsuda 2004 (59)	NIDDM	231 (58)	60	MeanCC and MaxCC/Bif/ICA	0.89	n.p.	Yes with mean-IMT. No with max-IMT
58	Larsson 2005 (60)	Overt-CVD	109 (54)	60	CC (F)	0.76	No	No
Interleukins:								
3	Hulthe 2002 (38)	Healthy	365 (100)	58	CC/Bif/ICA (Comp) (F)	0.8	No (IL6)	n.p.
5	Leinonen 2004 (53)	Healthy	78 (62)	61	Max IMT	1.05	Yes (IL-6)	No (IL-6)
59	Nakamura 2005 (65)	Healthy	55 (42)	61	MM CC	0.7	No (IL-18)	n.r.
17	van der Meer 2002 (44)	Popul	714 (46)	67	CC/Bif/ICA	n.r.	No (IL-6)	No
24	Chapman 2004 (66)	Popul	1111 (50)	53	CC (plaque excl.) (F)	n.r.	Yes (IL-6)	No
27	Elkind 2005 (62)	Popul	141 (42)	67	MM CC/Bif/ICA (F+N)	0.89	Yes (IL-2), No (IL-1 β and IL-6)	Yes (IL-2)
30	Yamagami 2005 (68)	Popul	366 (49)	65	MM CC/Bif/ICA (F+N)	0.99	Yes (IL-18), Yes (IL-6)	Yes (IL-18)
60	Chapman 2006 (67)	Popul	1111 (50)	53	CC (plaque excl.) (F)	0.7	Yes (IL-18)	No
37	Manabe 2005 (27)	Hypertens	41 (49)	62	CC (plaque excl.) (F)	0.81	No (IL-6)	No (IL-6)
35	Choi 2004 (20)	Hypertens+healthy	186 (37)	48	CC R	0.62	No (IL-6)	n.p.
34	Sebestjen 2005 (25)	Lipid	72 (100)	46	MM CC/Bif/ICA (F)	0.86	Yes (IL-6)	No
61	Okopien 2001 (69)	Lipid+healthy	86 (56)	n.r.	CC	0.7	Yes (IL-6)	n.p.
42	Esposito 2004 (33)	NIDDM	401 (60)	56	CC	0.87	Yes (IL-6, IL-18)	Yes (IL-6) No (IL-18)
5	Leinonen 2004 (53)	NIDDM	239 (62)	61	Max IMT	1.19	No (IL-6)	n.p.
62	Aso 2003 (70)	NIDDM	103 (47)	60	MM CC	0.74	Yes (IL-18)	n.p.
59	Nakamura 2005 (65)	NIDDM	82 (42)	61	MM CC	0.86	Yes (IL-18)	n.r.
58	Larsson 2005 (60)	Overt-CVD	109 (54)	60	CC (F)	0.76	No (IL-6, IL-8)	No (IL-6, IL-8)
63	Jurcut 2005 (71)	Overt-CVD+healthy	60 (58)	61	IMT (generically defined)	n.r.	No (IL-18)	n.r.
Other inflammatory markers:								
5	Leinonen 2004 (53)	Healthy	78 (62)	61	Max IMT	1.05	Yes (hSAA)	Yes (hSAA)
64	Tabara 2003 (75)	Popul	325 (34)	71	CC R (F)	0.79	Yes (MCP-1)	No (MCP-1)

Table I. (Continued)

Progressive number of articles reviewed	First author, year of publication (reference)	Subjects ^a	n (male %)	Age (mean)	Location ^b	IMT (mm) ^c	Univariate correlation or association	Multivariate correlation or association
5	Leinonen 2004 (53)	NIDDM	239 (62)	61	Max IMT	1.19	No (hSAA)	n.p.
47	Takebayashi 2006 (76)	NIDDM	70 (47)	60	MM CC R	n.r.	No (MCP-1)	n.p.
58	Larsson 2005 (60)	Overt-CVD	109 (54)	60	CC (F)	0.76	No (hSAA) Yes (MCP-1)	No (hSAA) No (MCP-1)
Adhesion molecules:								
65	Hulthe 2002 (61)	Healthy	365 (100)	58	CC+Bif+CC/Bif/ICA (Comp) (F)	0.8	Yes (E-selectin with Bif) Yes (ICAM with Comp) No (VCAM)	No (ICAM, VCAM, E-selectin)
2	Holmlund 2002 (80)	Healthy	59 (54)	50	CC (F)	0.76	No (ICAM, VCAM, E-selectin)	n.r.
55	Skoog 2002 (57)	Healthy	96 (100)	50	CC (F+N)	0.86	Yes (E-selectin) No (ICAM; VCAM)	Yes (E-selectin) n.p. (ICAM; VCAM)
5	Leinonen 2004 (53)	Healthy	78 (62)	61	Max IMT	1.05	Yes (VCAM)	Yes (VCAM)
6	Moussavi 2004 (49)	Healthy	25 (58)	54	CC (F)	0.63	No (ICAM, VCAM, E-selectin)	No (ICAM, VCAM, E-selectin)
66	Su 2006 (81)	Healthy	118 (0)	58	CC/Bif (F)	0.76	n.p.	No (ICAM, VCAM)
67	Rohde 1998 (85)	Popul	92 (52)	65	Mean CC+Mean Bif+Max CC/Bif (Comp)	0.9	Yes (ICAM, VCAM)	ICAM (Yes with mean-CC, Yes with mean-Bif, No with Comp) VCAM (No with mean-CC, Yes with mean-Bif, Yes with Comp)
68	Bongard 2002 (83)	Popul	972 (53)	50	CC (plaque excl.) (F)	0.59	No (ICAM)	No (ICAM)
17	van der Meer 2002 (44)	Popul	714 (46)	67	CC/Bif/ICA	n.r.	No (ICAM, VCAM)	No (ICAM, VCAM)
23	Amar 2004 (84)	Popul	891 (53)	49	CC (plaque excl.) R (F)	0.59	Yes (ICAM)	n.p.
31	Ahluwalia 2006 (82)	Popul	896 (53)	n.r.	CC (plaque excl.) (F)	0.59	n.r.	No (ICAM)
69	Bemelmans 2002 (87)	Lipid	103 (n.r.)	55	CC/Bif/ICA (F)	0.83	Yes (ICAM)	Yes (ICAM)
70	Paiker 2000 (88)	(FH+/-)	26 (52)	35	IMT (generically defined)	1.4	No (ICAM, VCAM, E-selectin)	n.r.
71	Karasek 2005 (92)	(FCH families)	82 (46)	38	CC (plaque excl.) (F)	0.64	Yes (ICAM), No (VCAM)	n.p.

Table I. (Continued)

Progressive number of articles reviewed	First author, year of publication (reference)	Subjects ^a	n (male %)	Age (mean)	Location ^b	IMT (mm) ^c	Univariate correlation or association	Multivariate correlation or association
72	Malmqvist 2002 (89)	Hypertens	149 (89)	54	CC (F)	0.89	n.p.	No (ICAM, VCAM, E-selectin)
38	Zavaroni 2006 (28)	Hypertens	63 (49)	55	CC (F)	0.96	Yes (ICAM,) No (VCAM, E-selectin)	n.p.
73	Kawamura 1998 (90)	NIDDM	82 (40)	70	MM CC (plaque excl.)	1.11	No (ICAM, E-selectin), Yes (VCAM)	n.p.
5	Leinonen 2004 (53)	NIDDM	239 (62)	61	Max IMT	1.19	No (ICAM, VCAM, E-selectin)	No (ICAM, VCAM, E-selectin)
6	Moussavi 2004 (49)	NIDDM	40 (58)	54	CC (F)	0.63	No (ICAM, VCAM, E-selectin)	No (ICAM, VCAM, E-selectin)
39	Balletshofer 2005 (30)	NIDDM risk	81 (44)	33	CC (F)	0.5	Yes (ICAM)	Yes (ICAM)
74	Otsuki 1997 (94)	NIDDM+healthy	101 (56)	63	Mean CC and Max CC/ICA/ECA	n.r.	Yes (VCAM)	Yes (VCAM)
75	Troscid 2006 (91)	CVD risk	563 (100)	70	MM CC (F)	0.93	No (ICAM, VCAM, E-selectin)	No (ICAM, VCAM, E-selectin)
76	Hashimoto 2003 (86)	CVD risk	301 (53)	64	Max IMT (F+N)	1.9	Yes (ICAM)	Yes (ICAM)
77	Kondo 2005 (12)	CVD risk	192 (51)	63	Max IMT (F)	1.74	No (ICAM)	n.p.
58	Larsson 2005 (60)	Overt-CVD	109 (54)	60	CC (F)	0.76	Yes (VCAM)	No (ICAM, VCAM, E-selectin)
78	De Caterina 1997 (93)	PVD+hypertensive+ healthy	33 (81)	57	Mean CC and Max CC/Bif (F)	n.r.	Yes (VCAM, ICAM)	Yes (VCAM)
Von Willebrand factor (vWF):								
79	Agewall 1994 (97)	Healthy	51 (100)	69.5	Max IMT	0.99	No	n.p.
80	Ramsis 1998 (98)	Healthy	36 (100)	44	CC (F)	n.r.	No	No
81	Metcalf 2000 (99)	Healthy	11964 (45)	55	CC/Bif/ICA	0.66	No	No
9	Beloqui 2005 (40)	Healthy	291 (77)	58	CC (plaque excl.) (F+N)	0.71	No	n.p.
55	Skoog 2002 (57)	Healthy (no-smokers)	96 (100)	50	CC (F+N)	0.86	Yes	n.p.
82	Wu 1992 (100)	Popul (yes/no carot. ath)	770 (60)	56.2	CC/Bif/ICA (Comp) (F)	n.r.	No	No
83	Folsom 1993 (104)	Popul (total and w)	13332 (n.r.)	n.r.	Mean CC/Bif/ICA (Comp) (F)	n.r.	No in total, Yes in w	Yes
84	Lee 1998 (101)	Popul (m and w)	547 (100) and 559 (0)	n.r.	MaxCC (F)	0.85 and 0.79	No	No
68	Bongard 2002 (83)	Popul	972 (53)	50	CC (plaque excl.) (F)	0.59	No	No

Table I. (Continued)

Progressive number of articles reviewed	First author, year of publication (reference)	Subjects ^a	n (male %)	Age (mean)	Location ^b	IMT (mm) ^c	Univariate correlation or association	Multivariate correlation or association
18	Wang 2002 (102)	Popul	3173 (48)	47	MM CC/Bif/ICA (F+N)	n.r.	n.p.	Yes
23	Amar 2004 (84)	Popul	891 (53)	49	CC (plaque excl.) R (F)	0.59	Yes	n.p.
85	Sakata 2004 (103)	Popul (m and w)	245 (100) and 277 (0)	62	CC (F+N)	0.89 and 0.82	Yes	No in m, Yes in w
38	Zavaroni 2006 (28)	Hypertens	63 (49)	55	CC (F)	0.96	No	n.p.
46	Tajiri 2005 (36)	NIDDM	295 (55)	60	CC (F)	0.7	Yes	No
81	Metcalfe 2000 (99)	NIDDM or NIDDM+healthy	921 (45) and 12897 (45)	55	CC/Bif/ICA	0.71	No in NIDDM; n.p. in the total group	No in NIDDM; Yes in the total group
73	Otsuki 1997 (94)	NIDDM+healthy	64 (37.5)	60	Mean CC and Max CC/ICA/ECA	n.r.	No	n.r.
79	Agewall 1994 (97)	(High-risk patients)	129 (100)	69.5	Max IMT	1.11	No	n.p.
55	Skoog 2002 (57)	Smokers	96 (100)	50	CC (F+N)	0.86	Yes	No
77	Kondo 2005 (12)	CVD risk	192 (51)	63	Max IMT (F)	1.74	No	n.p.
86	Paramo 2005 (105)	CVD risk	857 (80)	54	IMT	n.r.	Yes	Yes
75	Troscid 2006 (91)	CVD risk	563 (100)	70	MM CC (F)	0.93	No	No
78	De Caterina 1997 (93)	PVD+hypertens+ healthy	33 (81)	57	Mean CC and Max CC/Bif (F)	n.r.	No	No
Matrix metalloproteinases and tissue inhibitors of metalloproteinases:								
87	Zureik 2005 (107)	Popul	238 (100)	57	CC (plaque excl.) (F)	0.722	Yes (TIMP-1) No (MMP-3, MMP-9)	n.p.
88	Beaudeux 2003 (153)	Lipid	52 (86.5)	50	CC (plaque excl.)	0.61	n.r.	No (MMP-3, MMP-9, TIMP-1)
Fibrinogen:								
79	Agewall 1994 (97)	Healthy	51 (100)	69.5	Max IMT	0.99	No	n.r.
89	Sosef 1994 (110)	Healthy	121 (53)	35	CC (F)	0.52	Yes	No
90	Lavrencic 1996 (111)	Healthy	28 (43)	20.4	MM CC/Bif/ICA (F)	0.49	No	n.p.
80	Ramsis 1998 (98)	Healthy (IMT > 1.1 vs < 1.1 mm)	36 (100)	44	CC (F)	n.r.	No	n.p.
91	Vrtovec 1999 (112)	Healthy	30 (100)	44	MM CC/Bif/ICA (Comp) (F)	0.96	No	n.p.
81	Metcalfe 2000 (99)	Healthy	11964 (45)	55	CC/Bif/ICA	0.66	Yes	Yes
9	Beloqui 2005 (40)	Healthy	291 (77)	58	CC (plaque excl.) (F+N)	0.71	Yes	Yes
4	Halenka 2004 (24)	Healthy	40 (46)	39	CC (plaque excl.) (F)	0.6	No	No
82	Wu 1992 (100)	Popul (yes/no carot ath)	770 (60)	56.2	CC/Bif/ICA (Comp) (F)	n.r.	Yes	Yes
83	Folsom 1993 (104)	Popul men	n.r. (44)	n.r.	Mean CC/Bif/ICA (Comp) (F)	n.r.	Yes	Yes
92	Joensuu 1994 (120)	Popul	60 (100)	44	MaxCC	1.2	Yes	Yes

Table I. (Continued)

Progressive number of articles reviewed	First author, year of publication (reference)	Subjects ^a	n (male %)	Age (mean)	Location ^b	IMT (mm) ^c	Univariate correlation or association	Multivariate correlation or association
93	Folsom 1998 (124)	Popul (m and w)	1474 (100) and 1985 (0)	n.r.	CC/Bif/ICA (Comp) (F)	n.r.	n.p.	No
84	Lee 1998 (101)	Popul (m and w)	547 (100) and 559 (0)	n.r.	Max CC (F)	0.85 and 0.79	Yes in m, No in w	Yes in m, No in w
94	Ebrahim 1999 (119)	Popul (m and w)	418 (100) and 367 (0)	66	CC and Bif (F)	0.84/1.69 and 0.75/1.5 for CC and Bif (and for m and w) respectively	n.p.	In m Yes in both CC and Bif. In w No in CC, Yes in Bif
95	Ferrières 1999 (125)	Popul (m, w and m+w)	536 (100), 477 (53) and 1013 (53)	49	CC (F)	0.61, 0.58 and 0.6	Yes in m., n.r. in w and No in total group	No
96	Poredos 1999 (121)	Popul	122 (50)	34	CC/Bif (F)	0.56	Yes	Yes
97	Mavri 2001 (130)	Popul	62 (0)	40	CC/Bif (F)	0.76	Yes	n.p.
98	Stensland-Bugge 2001 (8)	Popul (m and w)	2984 (100) and 3373 (0)	63	CC/Bif R (F+N)	0.91 and 0.83	Yes in m. No in w	Yes in m. No in w
68	Bongard 2002 (83)	Popul	972 (53)	50	CC (plaque excl.) (F)	0.59	No	No
16	Sitzer 2002 (43)	Popul	1018 (50)	54	CC (F)	n.r.	Yes	Yes with CC. No with Bif and ICA
20	de Maat 2003 (45)	Popul	695 (47)	60	CC/Bif R (F+N)	0.72	n.p.	No
99	Martinez-Vila 2003 (122)	Popul	135 (84)	50	MM CC	0.78	Yes	Yes
22	Muscari 2003 (126)	Popul	288 (100)	59	Max Bif (F)	2.29	Yes	Yes
23	Amar 2004 (84)	Popul	891 (53)	49	CC (plaque excl.) R (F)	0.59	Yes	n.p.
24	Chapman 2004 (66)	Popul	1111 (50)	53	CC (F)	n.r.	Yes	No
26	McDonald 2004 (47)	Popul	218 (44)	37	CC	0.63	Yes	Yes
100	Paramo 2004 (123)	Popul	519 (81)	56	CC (plaque excl.) (F+N)	0.74	Yes	Yes
29	Mitusch 2005 (127)	Popul	1032 (52)	n.r.	Mean CC and Max CC	0.84	Yes	No
90	Lavrencic 1996 (111)	FH or FH+healthy	28 (43) and 56 (43)	20	MM CC/Bif/ICA (F)	0.71 and 0.6	No	n.p.
101	Montecchi 2001 (113)	Lipid	41 (27)	50	Mean CC and Max CC (plaque excl.) (F)	0.71 (mean) 0.82 (max)	Yes	Yes
4	Halenka 2004 (24)	Lipid or lipid+healthy	82 (46) and 122 (46)	39	CC (plaque excl.) (F)	0.7 and 0.65	No in Lipid. Yes in Lipid+healthy	No
34	Sebestjen 2005 (25)	Lipid (combined hyperlip)	72 (100)	46	MM CC/Bif/ICA (F)	0.86	No	No
102	Raal 1999 (117)	Lipid (FH)+healthy	62 (52)	29	CC	0.95	Yes	No
103	Marchesi 1999 (114)	Hypertens	200 (62)	46	CC Mean CC and Max CC (F)	0.72 (mean) 0.85 (max)	Yes	n.p.
79	Agewall 1994 (97)	Hypertens	129 (100)	69.5	Max IMT	1.11	Yes	Yes
104	Rossl 2001 (118)	hypertens+healthy	177 (n.r.)	n.r.	IMT	n.r.	No	n.p.
35	Choi 2004 (20)	hypertens+healthy	186 (37)	48	CC R	0.62	No	n.p.

Table I. (Continued)

Progressive number of articles reviewed	First author, year of publication (reference)	Subjects ^a	n (male %)	Age (mean)	Location ^b	IMT (mm) ^c	Univariate correlation or association	Multivariate correlation or association
105	Temelkova-Kurktschiev 2002 (115)	NIDDM risk	597 (48)	55	Mean CC and Max CC (plaque excl.) (F)	n.r.	Yes	Yes
40	Ahmad 2006 (31)	NIDDM risk (fam NIDDM)	38 (78)	30	CC/Bif and (CC+Bif)	0.51	Yes	No
41	Festa 2001 (32)	NIDDM and at risk (m, w and total)	652 (100), 801 (0) and 1453 (45)	55	CC and ICA	0.82 and 0.88 (of total group)	Yes just for CC in m	Yes just for CC in m
81	Metcalf 2000 (99)	NIDDM	921 (45)	55	CC/Bif/ICA	0.71	No	No
101	Montecchi 2001 (113)	NIDDM	43 (49)	59	MeanCC and MaxCC (plaque excl.) (F)	0.8 and 0.96	No	n.r.
47	Takebayashi 2006 (116)	NIDDM	70 (47)	60	MM CC R	n.r.	No	n.p.
91	Vrtovec 1999 (112)	Overt-CVD and overt-CVD+healthy	30 (100) and 60 (100)	45.5	MM CC/Bif/ICA (Comp) (F)	0.96	No	n.p.
53	Magyar 2003 (21)	Overt-CVD+healthy	100 (58)	48	CC (F)	0.9	Yes	Yes
Other hemostatic markers								
79	Agewall 1994 (97)	Healthy	51 (100)	69.5	Max IMT	0.99	No (PAI-1 and prothrombin F1+2)	n.p.
91	Vrtovec 1999 (112)	Healthy	30 (100)	44	MM CC/Bif/ICA (Comp) (F)	0.96	Yes (PAI-1). No (t-PA)	n.p.
89	Sosef 1994 (110)	Healthy	121 (53)	35	CC (F)	0.52	No (FVII)	No (FVII)
106	Paramo 2004 (129)	Healthy	181 (77)	56	CC (plaque excl.) (F+N)	0.77	Yes (prothrombin F1+2)	Yes (prothrombin F1+2)
90	Lavrencic 1996 (111)	Healthy, lipid and total group	28 (43), 28 (43) and 56 (43)	20	MM CC/Bif/ICA (F)	0.49, 0.71 and 0.6	No (PAI-1), Yes (TFPI) in healthy	n.p. (PAI). No (t-PA) in Lipid+Healthy
97	Mavri 2001 (130)	Popul	62 (0)	40	CC/Bif (F)	0.76	No (PAI-1 and t-PA)	n.p.
20	de Maat 2003 (45)	Popul	695 (47)	60	CC/Bif R (F+N)	0.72	n.p.	No (PAI-1, t-PA, FVII)
83	Folsom 1993 (104)	Popul	13332 (n.r.)	n.r.	Mean CC/Bif/ICA (Comp) (F)	n.r.	No (FVII, FVIII, ATIII)	n.r.
92	Joensuu 1994 (120)	Popul	60 (100)	44	MaxCC	1.2	No (Antithrombin III)	No (Antithrombin III)
93	Folsom 1998 (124)	Popul (m and w)	1464 (100) and 1956 (0)	n.r.	CC/Bif/ICA (Comp) (F)	n.r.	(PAI): n.p. in men, No in w	(PAI): No in m, n.r. in w
85	Sakata 2004 (103)	Popul (m and w)	245 (100) and 277 (0)	62	CC (F+N)	0.89 and 0.82	No (PAI-1), Yes (TFPI)	Yes (PAI-1) in m. No (TFPI) in w

Table I. (Continued)

Progressive number of articles reviewed	First author, year of publication (reference)	Subjects ^a	n (male %)	Age (mean)	Location ^b	IMT (mm) ^c	Univariate correlation or association	Multivariate correlation or association
84	Lee 1998 (101)	Popul (m and w)	547 (100) and 559 (0)	n.r.	MaxCC (F)	0.85 and 0.79	No (t-PA)	No (t-PA)
94	Ebrahim 1999 (119)	Popul (m and w)	418 (100) and 367 (0)	66	CC and Bif (F)	0.84 and 1.96 (m). 0.75 and 1.5 (w)	n.p.	No (FVII)
34	Sebestjen 2005 (25)	Lipid	72 (100)	46	MM CC/Bif/ICA (F)	0.86	No (PAI-1, t-PA), Yes (TFPI)	Yes (TFPI)
107	Jeng 1999 (132)	Hypertens	175 (52)	57	CC/Bif (F)	0.92	n.p.	No (PAI-1), Yes (t-PA)
103	Marchesi 1999 (114)	Hypertens	200 (62)	46	MeanCC (F)	0.7223	Yes (PAI-1)	Yes (PAI-1)
38	Zavaroni 2006 (28)	Hypertens	63 (49)	55	CC (F)	0.96	No (PAI-1)	n.p.
79	Agewall 1994 (97)	(High-risk patients)	129 (100)	69.5	Max IMT	1.11	No (PAI-1) No (prothrombin F1+2)	n.p.
82	Wu 1992 (100)	Popul (yes/no carot ath)	770 (60)	56.2	CC/Bif/ICA (Comp) (F)	n.r.	No (FVIII), Yes (FVII, antithrombin III)	Yes (ATIII)
75	Troscid 2006 (91)	CVD risk	563 (100)	70	MM CC (F)	0.93	No (t-PA)	No (t-PA)
91	Vrtovec 1999 (112)	Overt-CVD and overt-CVD+healthy	30 (100) and 60 (100)	45	MM CC/Bif/ICA (Comp) (F)	0.96	No (PAI). No (t-PA) in overt-CVD. Yes (t-PA) in total group	n.p.

^a Healthy=healthy subjects; Popul=population-based studies; Lipid=hyperlipidemic patients; Hypertens.=hypertensive patients; NIDDM=noninsulin-dependent diabetes mellitus; CVD=cardiovascular disease. ^b All IMT measurements were performed bilaterally, unless L (left) or R (right) is indicated. When Max or Mean-Max instead of Mean carotid IMT was measured, this is stated in the table. Measurements were performed on the far wall (F) or near wall (N), or far wall and near wall (F+N), not indicated if not stated in the text. (Comp)=composite; (m)=men; (w)=women; MM=mean-max; ^c The IMT values always represent mean CC IMT except if CC IMT is not measured. When different IMT values were reported for different subpopulations, these were averaged. n.r.=performed but not reported; n.p.=not performed; MS=metabolic syndrome; FCH=Familial combined hyperlipidemia; IMT=intima media thickness; Carotid ath=carotid atherosclerosis; hSAA=human serum amyloid A; FVII=Factor VII; ATIII=Antithrombin III.

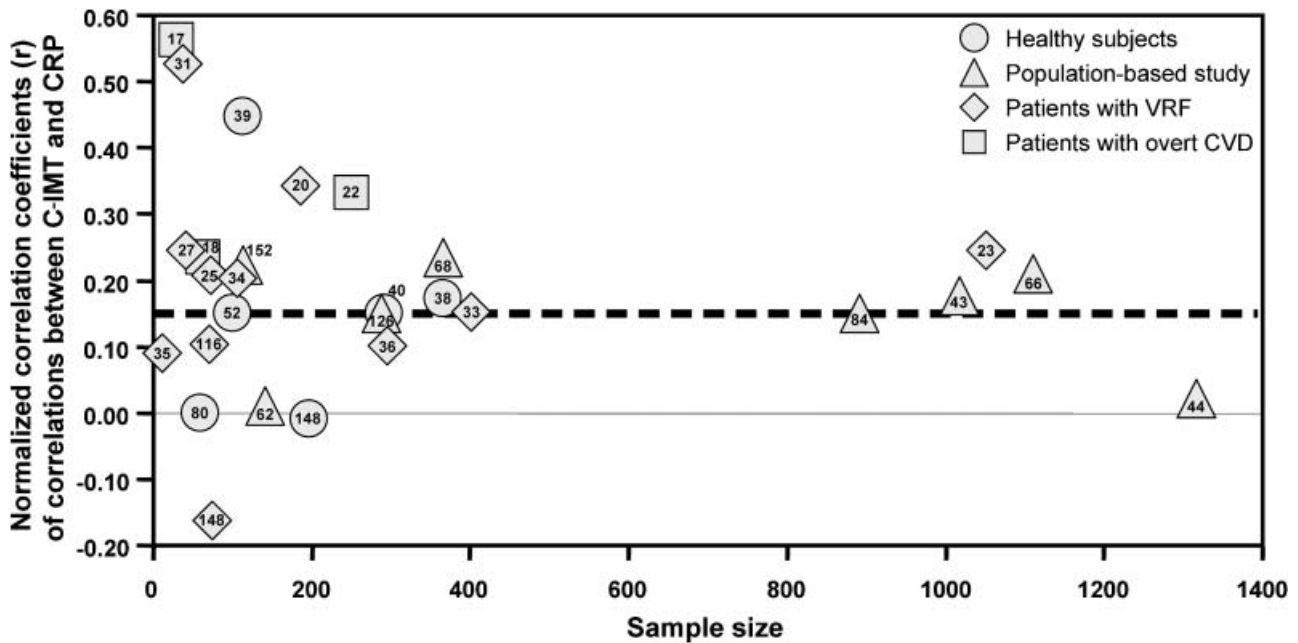


Figure 1. Funnel plots of univariate correlations between C reactive protein (CRP) and carotid-intima media thickness (C-IMT) obtained by plotting univariate correlation coefficients against the sample size of groups studied. Dashed lines indicate the overall effect observed in the meta-analysis. Publication bias would be suspected if there were a cluster of small studies on the upper left side of the graph not balanced by a similar cluster in the lower left side. Numbers within (or very close to) markers are references. VRF, vascular risk factors. CVD, cardiovascular diseases.

healthy subjects (38–41) and in patients with overt CVD (17–19) the number of significant associations (4 out of 11, and 3 out of 3, respectively) was also higher than <1 expected by chance, the number of groups considered was too small for statistical analysis.

In the 59 groups in which multivariate analyses have been performed (17,19,20,22–34,36–38, 40–42,44,46–49,51,53,55,57,58,60–62,64,65), the association between CRP and C-IMT was significant in 20 groups (29,30,32,33,36,42–48) (versus 3 expected by chance, $P < 0.001$ by Fisher's exact test).

No significant multivariate relationships were observed in studies performed in healthy subjects ($n=10$) (24,29,38–41,49–52), whereas significant associations were observed in 8 out of 24 groups with VRFs (versus 1 expected, $P < 0.03$) (29,30,32,33,36,7), in 11 out of 23 from general population groups (versus 1 expected, $P < 0.002$) (42–47), and in the single study performed in subjects with overt CVD (48). No trend between the atherosclerotic burden as defined above and the prevalence of significant associations between CRP and C-IMT was observed.

Studies showing significant univariate associations had a higher proportion of males (51.3%; $P < 0.0001$), whereas females were more represented in negative studies (52%; $P < 0.01$). The age or the

prevalence of hypertension was similar in studies showing or not showing significant associations. Among patients with VRF, a higher prevalence of significant univariate associations was found in noninsulin-dependent diabetes mellitus (NIDDM) (6 out of 12 versus <1 expected just by chance, $P < 0.0001$) but not in hyperlipidemics (1 out of 3) or hypertensives (1 out of 4).

The mean value of total and LDL-cholesterol of groups showing univariate associations was significantly higher than in groups showing no associations (5.59 ± 0.48 versus 5.13 ± 0.73 mmol/L, $P = 0.013$; and 3.6 ± 0.37 versus 3.12 ± 0.52 mmol/L, $P = 0.002$, respectively).

Figure 2 shows the proportion of significant univariate associations between C-IMT and CRP according to the sample size. Beyond showing the general statistical concept that the smaller the relation between two variables, the larger the sample size required to prove it as significant, the lack of an excess of positive associations in small studies (first bars) further suggests the absence of an important publication bias.

With multivariate analyses, we found only a higher concentration of fasting glucose among groups showing positive associations (7.66 ± 2.05 versus 5.92 ± 1.34 mmol/L, $P = 0.002$).

The relationship between C-IMT and CRP in obese subjects (body mass index ≥ 30) was

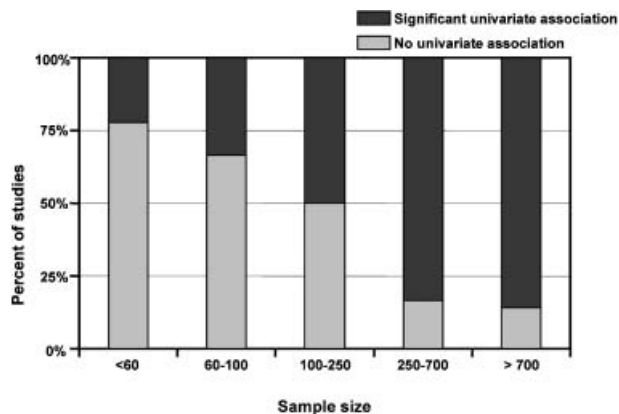


Figure 2. Percentage of studies with and without univariate association between C reactive protein (CRP) and carotid-intima media thickness (C-IMT).

investigated in five studies only (32,49,50,53,54), and all failed to show multivariate associations between the two variables. However, stratifying all the groups considered in this review into tertiles of body mass index (BMI) (whenever this information was available), a higher proportion of studies showing a significant multivariate association between CRP and C-IMT was observed in the highest BMI tertile.

Tumor necrosis factor α

Tumor necrosis factor α (TNF α) is a proinflammatory cytokine predominantly produced by monocytes/macrophages, endothelial cells, and smooth muscle cells (55). It acts via TNF receptors on target cells. Subjects with elevated TNF α levels are at increased risk of coronary death and recurrent myocardial infarction, independently of other VRFs (56).

A few studies have so far investigated the role of TNF α as a determinant of C-IMT (25,31,38,57–60). One out of two studies performed in healthy men (57,61) showed a significant univariate association, not, however, confirmed after data adjustment for metabolic risk indicators for coronary artery disease (57). Forcing TNF α into the model, TNF α accounted for 6% of C-IMT variability (57). In two population-based studies (58,62), no correlation between C-IMT and TNF α was found either before or after data adjustment for VRF.

Among studies performed in patients with VRFs (25,31,59), no correlation was found either in first-degree relatives of patients with NIDDM (31) or in patients with hyperlipidemia (25). A significant correlation was observed, however, in patients with NIDDM after data adjustment for age (59). In patients with manifest or suspected coronary artery disease (CAD) no correlation was found (60).

Interleukins

Interleukins are a class of cytokines that play an important role in the initiation and control of inflammatory processes (63). Interleukins are involved in cell activation, differentiation, chemotaxis, and proliferation in a broad range of cell types (64). Different interleukins are thought to play a role in the atherosclerotic process (63). Associations with C-IMT have been studied for IL-1 β , IL-2, IL-6, IL-8, and IL-18. Among three studies performed in healthy men (53,61,65), only one reported a univariate correlation between IL-6 and C-IMT (53). In population-based studies, no association between either IL-1 β or IL-6 and C-IMT was observed in multivariate analyses (44,62,66–68). The correlation between C-IMT and IL-18 was observed in one (68) but not in another study (67). A positive and significant association between IL-2 and C-IMT was also reported, which persisted after data adjustment for VRF (62).

Several studies have investigated patients with VRFs. In dyslipidemic patients, C-IMT was significantly correlated with IL-6 in univariate but not multivariate analyses (25,69). In hypertensive patients, the correlation with IL-6 was not significant (20,27) even after data adjustment for VRF (27). In NIDDM patients, both a significant correlation (33) and no correlation (53) between C-IMT and IL-6 were observed. A univariate correlation with C-IMT was found for IL-18 in three studies (33,65,70), but in none of these were the results confirmed by multivariate analyses.

Two studies in patients with overt CVD showed no correlation between IL-6, IL-8 or IL-18 and C-IMT (60,71), even though a negative correlation between IL-6 and carotid lumen diameter—another index of carotid atherosclerosis—was observed in multivariate analysis (60).

Other inflammatory markers

Inflammatory molecules such as monocyte chemoattractant protein-1 (MCP-1), CD40 ligand (CD40L), and serum amyloid A (SAA) have also been considered as predictors of CVD (72–74), but their relationship with C-IMT has not been extensively investigated. To the best of our knowledge, only one study provided data in healthy subjects showing a significant correlation between C-IMT and SAA (53). In a general population, MCP-1 was related to C-IMT in univariate analysis (75).

In patients with VRFs, two studies in NIDDM patients have been reported. In one, SAA did not correlate with maximum C-IMT in univariate analysis but correlation was significant after data

adjustment for age, sex, smoking, and body mass index (53). In the other, no correlation between C-IMT and MCP-1 was found (76). Finally, a single study carried out in patients with overt CVD reported that C-IMT was not correlated with MCP-1 or SAA after data adjustment for VRF (60).

Markers of endothelial damage

Adhesion molecules

Adhesion molecules are responsible for the attraction and adhesion of monocytes to the activated endothelium and for their transendothelial migration. Both intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1) have been associated with atherosclerosis development (77,78). E-selectin is produced by endothelial cells and mediates endothelial rolling of leukocytes. The role of E-selectin in CVD is less clear, although it has been suggested to be particularly significant in diabetics (79).

Among the six studies performed in healthy subjects (49,53,57,61,80,81), three found no correlation between C-IMT and ICAM or VCAM in multivariate analysis (49,61,81), whereas one reported a significant multivariate correlation with VCAM (53). Two further studies found no correlation in univariate analyses (57,80). In healthy subjects, no correlation between C-IMT and E-selectin was found in multivariate analyses (49,53,61); in the unique study in which E-selectin was the strongest predictor of C-IMT, the association was lost when TNF α was added as a forced variable into the multivariate model (57).

Several population-based studies have investigated the correlation between C-IMT and ICAM or VCAM. Three studies did not identify any correlation (44,82,83), but two other studies showed correlations between both soluble markers and mean C-IMT (84,85) even after data adjustment for VRF (85). VCAM also correlated with maximum C-IMT, but the correlation was lost after data adjustment for age (85).

For patients with VRFs, both significant (28,30,86,87) and nonsignificant correlations (12,49,53,88–91) were found between C-IMT and ICAM. In mildly hypercholesterolemic patients, ICAM was related to C-IMT in both univariate and multivariate analyses (87). Two studies in members of familial hypercholesterolemia (FH) families provided contrasting results (88,92): Paiker et al. (88) found no correlation between C-IMT and ICAM, VCAM or E-selectin, whereas Karasek et al. (92) found such a relationship with

ICAM but not VCAM; however, no multivariate analyses were reported. Contradictory data were also found in hypertensives (28,89,93). No relationship was observed in NIDDM patients between C-IMT and ICAM, VCAM or E-selectin (49,53,90). In two studies, one performed in patients at risk of NIDDM (30) and one in NIDDM patients and healthy subjects pooled together, (94) multivariate analysis confirmed the correlation between C-IMT and ICAM (30) and VCAM (94).

In the only study carried out in patients with overt CVD, no correlation between C-IMT and ICAM or VCAM was detected by multivariate analysis (60).

Von Willebrand factor

Von Willebrand factor (vWF) is a glycoprotein produced by endothelial cells that is involved in thrombus formation during vascular injury and is regarded as a well established marker of endothelial dysfunction (95). In addition, it has been shown to be related to the progression of CVD (96).

Among studies performed in healthy subjects (40,57,97–99), only one provided evidence of univariate correlation between vWF and C-IMT (57). Three out of the seven population-based studies found no univariate or multivariate correlation (83,100,101). Among the others, one reported only a univariate correlation (84), one a multivariate correlation (102), and two a multivariate correlation confined to women (103,104).

In patients with VRFs, both a correlation (99,105) and no correlation (36,57,91) have been reported. No correlation between C-IMT and vWF was found in hypertensive patients with peripheral vascular disease (93).

MMPs and TIMPs

Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes, mainly secreted by macrophages and smooth muscle cells, which regulate the physiological remodeling of vascular extracellular matrix. Their activity is inhibited by tissue inhibitors of metalloproteinases (TIMPs), also produced by macrophages. Their involvement in various steps of atherogenesis is well established (106).

Although more than 20 members of the MMP and 4 of the TIMP families are known, only MMP-3, MMP-9, TIMP-1, and TIMP-2 have been investigated for their relationships with C-IMT. To the best of our knowledge, no studies in healthy subjects have been performed. In a population-based study, TIMP-1, MMP-3, and MMP-9 were not found to

be associated with C-IMT in multivariate analysis (107). With respect to studies including patients with VRFs, no association was found between MMP-3, MMP-9, TIMP-1 and TIMP-2 and C-IMT in dyslipidemic patients (108). In this study, however, MMP-3 and TIMP-1 concentrations were significantly associated with obstructive carotid arterial lesions (10%–25% luminal obstruction). Studies in patients with overt CVD were not found.

Markers of hemostasis

Fibrinogen

Fibrinogen, a large glycoprotein produced by the liver, plays a role in platelet aggregation, endothelial cell injury, and plasma viscosity. A high fibrinogen plasma concentration is associated with increased cardiovascular risk and increases the prediction of cardiovascular events (109).

The relationship between fibrinogen and C-IMT was investigated in 59 groups within 39 studies (8, 20, 25, 32, 36, 38–40, 42, 45, 50, 51, 56, 57, 63, 69, 94, 107–111, 113, 119–134). A significant univariate correlation/association was found in 33 groups (55.9%) (8, 20, 25, 32, 38–40, 42, 45, 56, 57, 69, 107, 109–111, 113, 120, 122, 124–130, 132, 133), when fewer than 3 (5%) were expected by chance alone, according to the null hypothesis of no correlation between the two variables ($P < 0.0001$ by Fisher's exact test) and assuming no publication bias.

Figure 3 shows the funnel plot analysis of univariate correlations between fibrinogen and C-IMT. The overall results support a significant positive correlation between C-IMT and fibrinogen, and no relevant publication bias can be detected.

The number of groups with significant univariate associations between fibrinogen and C-IMT (8, 32, 38–40, 42, 45, 111, 113, 120, 122, 125, 126, 128, 129) was higher than expected in population-based cohorts (17 out of 21; versus 1 expected by chance, $P < 0.0001$ by Fisher's exact test) and in patients with VRF (31, 32, 97, 113–115) (9 out of 20 versus 1 expected by chance, $P < 0.0001$ by Fisher's exact test). Although in healthy subjects the number of positive associations (3 out of 8) (40, 99, 110) was also higher than the 5% expected by chance alone, the number of groups considered was too small for statistical consideration. In the single study performed in patients with overt CVD, no significant association was found (112).

At least four studies (8, 32, 101, 119) showed a correlation between fibrinogen and C-IMT in men but not in women; in addition, females were more represented in negative studies (52.1%; $P < 0.0001$). The mean age was similar in positive and negative studies, whereas the mean systolic and diastolic blood pressures were higher in positive than in negative studies (+12.7 and +6.8 mmHg, $P = 0.003$ and $P = 0.025$, respectively). The mean value of total and fasting glucose and BMI of groups showing univariate or multivariate associations was not

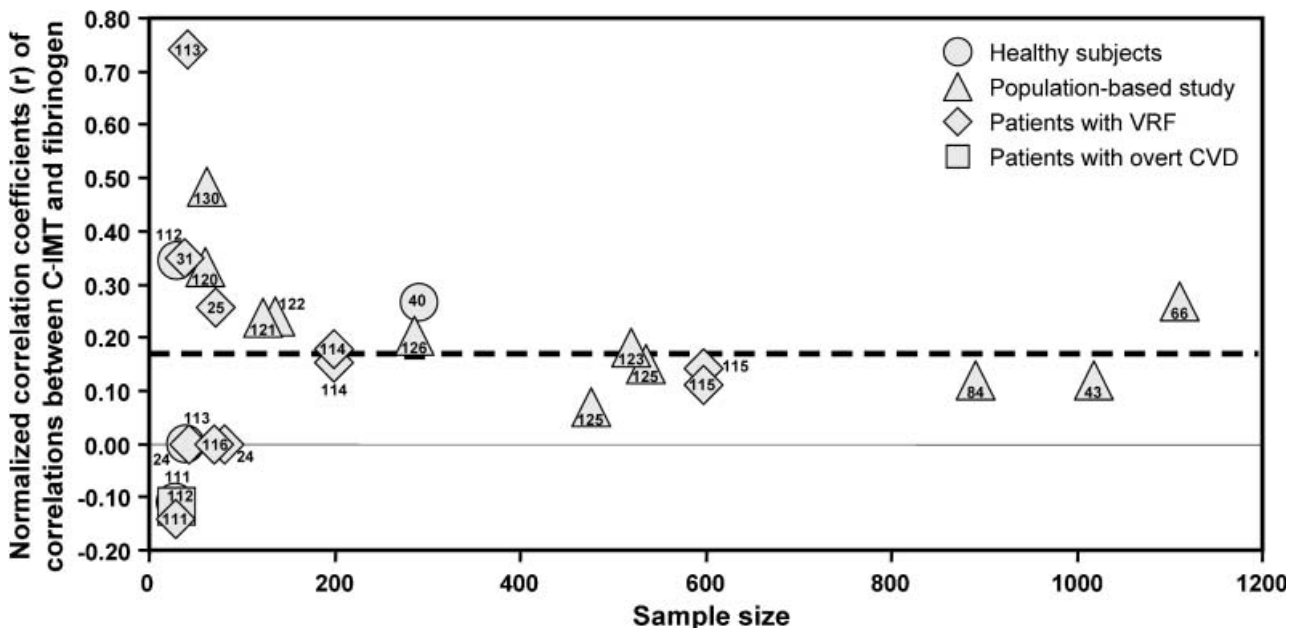


Figure 3. Funnel plots of univariate correlations between fibrinogen and carotid-intima media thickness (C-IMT) (see legend of Figure 1). VRF, vascular risk factors. CVD, cardiovascular diseases.

significantly different from that of groups showing no association, whereas LDL-cholesterol was higher in groups showing multivariate association (3.59 ± 0.38 mmol/L versus 4.18 ± 0.5 mmol/L, $P=0.018$).

In contrast to CRP, the probability of finding a significant association was not related to sample size.

In the 49 groups within 29 studies (8,20,25,32,36,38,40,42,45,56,57,69,94,107,109–111,113,119–122,125,127–130,132,133) in which multivariate analyses was performed, the association between fibrinogen and C-IMT was significant in 23 groups (8,25,32,38,42,57,69,107,109–111,113,119,122,125,127–129,133) (versus 2.4 expected by chance alone, $P<0.0001$ by Fisher's exact test). A significant association was observed in 2 (40,99) out of 4 (24,40,99,110) groups of healthy subjects, in 13 (8,43,47,101,104,119–123) out of 27 groups (8,43,45,47,66,83,101,104,119–127) from the general population (versus 1.35 expected, $P<0.001$), and in 6 (32,97,113,115) out of 14 groups (24,31,32,97,99,113,115) with VRFs. No studies with overt CVD patients were available.

Other markers of hemostasis

Other soluble markers of hemostasis have been studied in relation to C-IMT, i.e. tissue plasminogen activator (t-PA), plasminogen activator inhibitor-1 (PAI-1), tissue factor pathway inhibitor (TFPI), prothrombin fragment F1+2 (F1+F2), factor VII, factor VIII, and antithrombin. All these markers may play a role in the development of CVD by modulating the balance between coagulation and fibrinolysis (128).

In healthy subjects, a correlation was found between F1+2 and C-IMT, explaining 6.5% of IMT variance (129). No correlation was observed between C-IMT and FVII (110). In population-based studies, C-IMT did not correlate with free TFPI, t-PA, FVII, FVIII, PAI-1 or antithrombin III (45,100,101,103,104,119,120,124,130). However, in one study C-IMT correlated with PAI-1, in men only (103). In combined hyperlipidemia, TFPI was a determinant of C-IMT variance (25), whereas t-PA and PAI-1 were not (25,111). In two studies in hypertensive patients, PAI-1 (114,131) and t-PA (132) were related to C-IMT; in other studies, no such association was found (28,132). In patients with carotid disease, C-IMT correlated with antithrombin III concentrations but not with factor VII or VIII (100). In coronary patients, t-PA and PAI-1 were not correlated to C-IMT in univariate analysis (112).

Considerations on protocols used to measure C-IMT

Table I clearly shows substantial heterogeneity among the protocols used to measure C-IMT in the studies reviewed. To evaluate whether this aspect could have influenced the relationship between C-IMT and the soluble markers considered, we recalculated the prevalence of groups showing significant associations after stratifying them according to the following aspects of the protocol used for C-IMT measurement: location (common carotid, bifurcation, internal carotid, or composite), outcomes (Mean-IMT, Max-IMT, or Mean Max-IMT), arterial wall (far wall, near wall, or both), carotid side (left plus right, or only right) and exclusion/inclusion of plaques. In these analyses, the prevalence of significant associations between C-IMT and fibrinogen was higher than expected when Mean-IMT and Max-IMT were utilized and much lower when Mean Max-IMT was used ($P<0.0001$ by chi-square). In addition, the prevalence of significant associations between C-IMT and CRP was higher than expected, with a P -value close to statistical significance (0.062 by chi-square), in studies excluding atherosclerotic plaques. No other significant differences between strata were observed.

Discussion

This review of data from 107 studies, addressing the relationship between carotid intima-media thickness and soluble markers of inflammation, endothelial damage or hemostasis, leads to the conclusion that C-IMT associates unequivocally only with fibrinogen and CRP plasma concentrations. Despite the marked heterogeneity of results present in the literature, the meta-analysis shows (dashed lines in the funnel plots) a predominance of studies with significant positive associations between C-IMT and CRP or fibrinogen. The symmetry of funnel plots, the constancy of the overall effect in the meta-analyses after exclusion of small studies, and the lack of an excess of positive associations in small studies (first bars of Figure 2) exclude publication bias, for both CRP and fibrinogen, as a significant effect on the univariate results.

Reliable meta-analysis could not be performed on multivariate results because of the variety of statistical methods used in each study to take confounding variables into account (partial correlation, multiple regression, covariance analyses, and others). However, independently of the statistical approach used, a multivariate association with C-IMT was observed in 20 out of 58 groups for CRP

and in 23 out of 49 groups for fibrinogen. Even though in multivariate analyses a publication bias cannot be completely excluded, the prevalence of studies linking C-IMT with both fibrinogen and CRP greatly exceeds the statistical threshold of 5% expected on the basis of the hypothesis of a null relationship between the variables considered and C-IMT (133). In addition, the lack of an excess of positive multivariate associations in small studies strongly suggests that also in this case publication bias could have only marginally affected the results.

Available data about the relationship between C-IMT and all other soluble markers are either scanty or mutually contradictory and in any case unconfirmed by multivariate analyses. In addition, a strong publication bias for all the variables considered was detected by funnel plot analyses (data not shown).

In an attempt to explain the incomplete agreement about the relationship between C-IMT and CRP or fibrinogen and the failure to establish a link between C-IMT and other soluble markers of atherogenic processes, we reexamined the literature, taking into account in addition the potential influence on these associations of the atherosclerotic burden and other characteristics of the patients included in the different studies.

We found no trend between the atherosclerotic burden, as defined in this study, and the prevalence of significant associations between C-IMT and any of the variables considered. A similar conclusion was reached by Moussavi et al. (49) in diabetic patients, showing that plasma concentrations of soluble markers are not directly linked to the atherosclerotic burden.

Sample size seems to be one of the most important determinants of the probability to find a significant univariate association between IMT and CRP, with an insufficient power when groups under study include less than 100–250 patients (Figure 2).

Among other patients' features that could potentially influence the correlation between C-IMT and soluble markers (i.e. gender, prevalence of risk factors, etc.), a predominance of men and a higher serum concentrations of fasting glucose and cholesterol (both total and LDL) was observed in groups showing a positive and significant relationship between C-IMT and CRP, thus suggesting a possible role of these variables in this association. However, the fact that a higher prevalence of significant associations was found in NIDDM patients but not in hyperlipidemics or hypertensives suggests that the IMT-CRP relationship is not influenced by the high-risk status per se, but that different risk factors may affect the relationship through specific pathways. Type 2 diabetes, for

example, is known to be associated with both increased C-IMT (134) and elevated hs-CRP levels (135).

A number of cross-sectional studies have shown an effect of obesity on both C-IMT (136) and CRP concentrations (137,138), and some authors even suggest that knowing the degree of obesity is essential for the interpretation of the relationship between CRP and severity of CAD (139). The literature reviewed here does not support this view; in fact, although a higher proportion of studies showed a significant multivariate association between C-IMT and CRP in the highest BMI tertiles of normal-weight groups, none of the studies specifically performed in obese patients detected multivariate associations between the two variables.

The higher proportion of women in studies showing no association between C-IMT and fibrinogen, as well as the higher mean values of systolic and diastolic blood pressure and LDL-C in studies reporting a significant association, suggest that gender, blood pressure, and cholesterol levels could affect the atherogenic role of fibrinogen.

Fibrinogen itself may influence the relationship between CRP and C-IMT. This possibility is supported by a study showing that the relationship between CRP and C-IMT disappears when fibrinogen is added into the multivariate model (43).

Besides the characteristics of the patients, other possible sources for the inconsistencies in conclusions about associations could be methodological. Since many factors may influence C-IMT, in determining the importance of an individual factor one should perform the analysis after data adjustment for all variables known to influence both the C-IMT and the variable. For instance, C-IMT increases with age more in men than in women (8), and gender differences also exist for soluble markers (140); thus, adjustments at least for age and gender are mandatory. Similarly, smoking is an important life-style determinant both of fibrinogen concentration (141) and of C-IMT (142), and adjustment for this life-style component is also vital. Unfortunately, as shown in Table I, these adjustments have rarely been made in the studies reviewed.

Again, since some soluble markers seem to relate better to localized plaques or complex lesions than to C-IMT (108,126,143), inconsistencies of reported results may depend on whether plaques are incorporated into the IMT measurement or not. For example, ICAM showed no correlation with C-IMT when plaques were not included in the IMT measurement (90), but correlated with plaque score (91) and Max-IMT but not with Mean-IMT (53).

Another source for the inconsistent relationship between C-IMT and soluble markers may be the site of the IMT measured in different studies. IMT is different in common carotid, bifurcation or internal carotid artery of the same individual (144). In addition, some VRFs are related to C-IMT in one segment but not in others (145,146). For example, since hypertension induces medial hypertrophy (generally not considered as atherosclerosis) mainly in the common carotid artery (93), it has been suggested that C-IMT should be measured as an atherosclerosis surrogate in hypertensives just at the bifurcation, because of the smaller number of smooth muscle cells at this site (147). Similarly, the outcomes (Mean-, Max- or Mean Max-IMT) as well as the arterial wall (far wall, near wall or both) or the carotid side (left plus right or just right) selected could also have influenced the relationship between C-IMT and inflammatory markers, endothelial damage, and hemostasis. This plausible possibility cannot be resolved by the data available.

A final issue is the validity of the funnel plot approach. The funnel plot has been advocated to scrutinize meta-analyses for publication bias (154). A common interpretation of funnel plots is that, when the points distribute around the overall effect asymmetrically and the plot loses the expected shape of an inverted funnel, then a publication bias may be present. It is worth acknowledging, however, that other factors besides publication bias (i.e. the different definition of precision and/or measured effect) may affect the shape of the funnel plot (155,156), thus raising concerns about the appropriateness of this statistical approach to exclude publication bias. Thus, in the absence of consensus on how the plot should be constructed, the existence of publication biases in the meta-analyses performed in the present study may not be definitely ruled out.

Conclusions

The present systematic review of studies addressing the association between subclinical carotid atherosclerosis and soluble markers of inflammation, endothelial damage or hemostasis shows that plasma CRP and fibrinogen levels are the variables most consistently related to C-IMT. No clear conclusions can be drawn for other soluble markers. Atherosclerotic burden does not appear to account for the heterogeneity of the findings reported in the literature. Among other patients' characteristics, gender, presence of NIDDM, and hypercholesterolemia were seen to influence the association between C-IMT and CRP, whereas blood pressure and hypercholesterolemia seem to affect the association

between C-IMT and fibrinogen. For the other soluble markers considered, the number of groups was too small for adequate statistical treatment.

Further studies using highly standardized protocols for C-IMT measurement and rigorous multivariate statistical approaches are needed to elucidate the still controversial relationship between soluble markers and C-IMT.

Acknowledgements

The first two authors contributed equally to the review.

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