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Chlamydia pneumoniae, Helicobacter pylori and cytomegalovirus infections and the risk of peripheral arterial disease in young women

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Abstract

Sero-epidemiological case control studies have observed positive relations between infections with *Chlamydia pneumoniae*, *Helicobacter pylori* or cytomegalovirus (CMV) and the occurrence of coronary artery disease (CAD) and stroke Moreover, positive relations between 'infection burden' and CAD and the role of inflammation have recently been described However, the relations between infection, inflammation and the occurrence of peripheral arterial disease (PAD) have not been reported so far We performed a multi-centre population-based case-control study, using serum samples of 228 young female PAD patients and 643 control women to determine IgG antibody titres and C-reactive protein The odds ratios for PAD in women with serological evidence for infection with *C pneumoniae, H pylori* or CMV were 2 0 (95% CI, 1 3–3 1), 1 6 (95% CI, 1 1–2 2) and 1 6 (95% CI, 1 1–2 3), respectively The cumulative number of infections was positively related to the risk of PAD, the odds ratio was 1 5 (95% CI, 1 0–2 4), 2 7 (95% CI, 1 6–4 4) and 3 5 (95% CI, 1 5–8 1) for women with one, two or three infections, respectively This increased risk, related to the 'infection burden', was found again in the subgroup of women with a high CRP level, but not in the subgroup with a low CRP level Infections might be a causal component in the development of PAD The risk of PAD is not only related to a single pathogen in particular, but also to the cumulative number of infections The positive relation between 'infection burden' and PAD was only found in women with a high CRP level, which indicates that inflammation might be involved in the process that leads to PAD

Keywords Atherosclerosis, Infection, Inflammation, Peripheral vascular disease, Risk factors

1. Introduction

In about half of the patients with atherosclerosis, conventional risk factors cannot explain the occurrence of the disease This observation indicates that additional, as yet undetected, risk factors attribute to the development of atherosclerosis Recently, studies have suggested that infection with *Chlamydia pneumoniae*, *Helicobacter pylori* or cytomegalovirus (CMV) might be independent risk factors for atherothrombotic diseases The role of these infectious agents in the development of CAD or stroke has frequently been studied by identifying infected patients through the presence of IgG antibodies [1] However, studies on the relation between

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C pneumoniae, *H pylori* and CMV and peripheral arterial disease (PAD) have not been reported so far

A mechanism by which infectious agents could possibly initiate or enhance atherogenesis is by triggering vascular inflammation Chronic infections may cause a low-grade inflammatory reaction, which is reflected by the C-reactive protein (CRP) concentration, that eventually causes atherogenesis [2–6] Therefore, exploration of the relations between infections and atherosclerosis, in combination with the CRP concentration, might provide insight in the pathophysiology of atherogenesis

We examined the relation between infections with *C pneumoniae*, *H pylori* or CMV and peripheral arterial disease in a population based case-control study of young women All patients that were included had at least a 50% reduction of the lumen in at least one major peripheral artery and had a negative history for cerebral or coronary heart disease Subsequently, we assessed the relation between the pathogen burden and PAD, and we verified the hypothesis that infections and atherogenesis might be linked through inflammation

2. Methods

2 1 Study design

This multi-centre, population based case-control study was approved by the local research ethics committees of the participating hospitals (see Acknowledgements)

2 2 Patients with peripheral arterial disease

Female patients were eligible if (a) they had been referred to one of the collaborating hospitals between 1st January 1990 and 31st December 1999, (b) had an angiographically confirmed diagnosis of PAD, (c) were aged 18–49 years at the time of referral, and (d) gave informed consent

PAD was considered if a patient presented with typical symptoms of intermittent claudication (cramping pain in the lower leg(s) during exercise) or with rest pain, non-healing ulcers or gangrene Intra-arterial angiography was performed in all patients A stenotic lesion of $>50\%$ reduction of the lumen in at least one major peripheral artery (distal abdominal aorta, common iliac artery, internal and external iliac artery, femoral artery, popliteal artery, anterior and posterior tibial artery, peroneal artery) was considered diagnostic for PAD

Of the 294 eligible PAD patients, 24 could not be located, despite extensive efforts Of the 270 patients who were successfully approached, 228 (78%) agreed to participate Little more than half (132) of these patients were referred between January 1990 and October 1995 and had participated in an earlier performed multicentre population-based case-control study in which the relations between the use of oral contraceptives and PAD were investigated by means of a questionnaire This case-control study consisted of three sub-studies, beside patients with PAD, the two other case groups included were stroke patients and patients with a myocardial infarction (MI) [7–9] In the group of women with PAD, those who also had a history of MI or stroke were excluded because having a history of MI or cerebral ischemia could have affected the decision to describe oral contraceptives In addition, one large control group of women was included to which each group of patients was contrasted

2 3 Controls

The population-based control group of women was recruited by random digit dialling (RDD), random phone numbers (in a certain area) were dialled and households were ascertained for eligible individuals (female, aged 18–49 years) who were subsequently asked to participate [10,11] This method resulted in the selection of controls who were approximately (5-year strata) the same age as the patients and who lived in the service areas of the participating hospitals In 1996, 1259 eligible women were reached by RDD, of whom 925 were included in the case control studies that investigated the relation between the use of oral contraceptives and MI, PAD or stroke [7–9] For the present analysis, 905 of these 925 women controls were approached again In total, 262 could not be reached or refused to participate again for a variety of reasons, e g fear for venepuncture or lack of time The remaining 643 women (71%) were included in this analysis

2 4 Data collection

Between 1st June 1998 and 1st May 2000, all participants had their blood pressure measured, donated non-fasting venous blood samples and handed in a structured questionnaire Blood pressure was measured semi-automatically by a physician (Omron*M1* OMRON Healthcare GmbH, Hamburg, Germany) at one point in time Serum or plasma were stored at -80 °C until processed Serum total cholesterol, triglyceride and glucose concentration were measured on a clinical analyser (Roche/Hitachi® 747) The HDL-cholesterol determination was performed on a different analyser (Roche/Hitachi® 911) The plasma CRP concentration was determined by a commercial EIA with a sensitivity of 0 2 mg/l (CRP EAI HS, Kordia, The Netherlands) Plasma CRP concentrations of 10 mg/l and above were classified as ≥ 10 mg/l

Data obtained from the questionnaire included current medication use and classical risk factors (body mass

index (BMI), smoking, history of hypercholesterolemia, history of diabetes, history of hypertension and family history of cardiovascular disease) We categorised smokers as current, former or never A positive history of hypercholesterolemia was defined by the use of cholesterol lowering medication or a serum total cholesterol $\geq 5\ 0$ mmol/l A positive history of diabetes was defined by the use of glucose lowering medication or a (non-fasting) serum glucose $\geq 11\ 0$ mmol/l

A positive history of hypertension was defined by the use of antihypertensiva or a systolic blood pressure $\geq$ 160 mmHg or a diastolic blood pressure ≥ 95 mmHg The socio-economic status was defined as the highest level of education attended by the participant primary school, secondary school or higher education/university

2 5 *Determination of IgG antibodies to infectious agents*

Immunoglobulin G antibodies to *C pneumoniae* were determined by a validated in-house enzyme immunoassay (EIA) [12–14] Briefly, *C pneumoniae* (strain TW-183) was propagated in six-well microtitre plates Elementary bodies were purified by centrifugation through a layer of 35% sodium diatrizoate and used to coat microtitre plates Antibodies to the chlamydial LPS were intentionally included, since they show the strongest association with cardiovascular disease All subjects were categorised into three groups according to their IgG title negative, positive and $1 < 6400$, and positive and $1 \geq 6400$ For the final analysis, the first two groups were pooled together This cut-off titre was previously shown to be associated with cardiovascular risk [15] Under the conditions described, this cut-off titre is approximately equivalent to an antibody titre of 1 64 in the micro-immunofluorescence test (MIF)

IgG antibodies to *H pylori* and cytomegalovirus were determined by the use of commercial EIA Positivity was defined according to the instructions of the manufacturer (Enzygnost® Anti-Helicobacter pylori II/IgG and Enzygnost® Anti-CMV/IgG, Dade Behring) All assays were performed by a single technician who was unaware of the origin of the samples (case or control)

2 6 *Statistical analysis*

The assumptions for the power calculation were the following (1) the prevalence of *C pneumoniae*, *H pylori* or CMV seropositivity would be $\approx 50\%$ in a population of this age, (2) the relative risk of PAD in persons with high level IgG antibodies compared with those without would be 2, (3) 150 PAD patients and 300 control women would be included, and (4) $\alpha \leqq 0\ 05$ would be accepted Then, a 2-fold increase in the risk of PAD would be detected with power 0 88

Mean or median values or proportions for cardiovascular risk factors were calculated for patients and control women separately The percentage of PAD patients seropositive for *C pneumoniae H pylori* or CMV was compared to the percentage of controls having a positive titre against the same infectious agent The crude and adjusted odds ratios, as estimates for the relative risk of PAD in women with a positive titre compared to women with a negative titre, were calculated using unconditional logistic regression Adjustment was made for the following potentially confounding factors age, smoking and educational level (low, middle or high)

The number of infections was determined for each participant The crude and the adjusted odds ratios for PAD were calculated in women with one, two or three infections compared to women without any infection The median CRP levels in women with none, one, two or three infections were calculated for PAD patients and healthy women separately The Kruskal–Wallis test was used to study the differences between the median CRP levels

Plasma CRP concentration was dichotomised with the overall median value (1 94 mg/l) as cut-off point To evaluate whether the pathogen burden and CRP level jointly affect the risk of PAD, we performed logistic regression analysis on two subgroups of women, one for all women with CRP at or below its median value and one for those above this value The following potentially confounding factors were included in the logistic regression models age, smoking, educational level (low, middle or high), BMI, history of hypercholesterolemia (yes, no), history of diabetes mellitus (yes, no) and history of hypertension (yes, no)

3. Results

Table 1 shows the characteristics of the 228 PAD patients and 643 control women Traditional risk factors for atherosclerosis were more prevalent in the group of patients compared to the control group of women The median plasma CRP concentration was higher in the PAD patients compared to the controls

Table 2 shows that high positive titres against *C pneumoniae* were found in 23% of the PAD patients compared to 13% of the control women, the prevalence of detectable IgG antibodies was much higher, namely 81 and 82% in the PAD patients and control women, respectively Some 40% of the patients were seropositive for *H pylori* compared to 26% of the controls and CMV seropositivity was found in 71% of the patients and 56% of the controls

The odds ratios and the 95% confidence intervals (CI) for PAD in women with a positive titre compared to women without are shown in Table 3 The crude odds ratio was 1 9 (95% CI, 1 3–2 8) for *C pneumoniae* 1 9 (95% CI, 1 4–2 6) for *H pylori* and 1 9 (95% CI, 1 4–

Table 1
Characteristics of PAD patients and control women

	PAD patients ($n = 228$)	Control women ($n = 643$)
Age in years (mean, S D)	48 0±7 0	44 9±8 3
BMI in kg/m^2 (mean, S D)	26 2±5 7	24 8±4 3
Smoking in % (n)		
–Current	60 (132)	33 (215)
–Former	35 (77)	34 (216)
–Never	5 (10)	33 (212)
History in % (n)		
–Hypercholesterolemia*	87 (194)	61 (390)
–Diabetes†	14 (31)	1 (8)
–Hypertension‡	60 (130)	23 (150)
Education in %		
–Primary school or less	22 (48)	9 (54)
–Secondary school	70 (153)	67 (429)
–Higher education or University	8 (18)	24 (156)
Mean systolic blood pressure in mmHg (mean, S D)	141 3±23 2	129 4±19 3
Mean diastolic blood pressure in mmHg (mean, S D)	84 6±12 1	82 1±11 4
Glucose in mmol/l (mean, S D)	6 53±4 38	4 13±1 39
Cholesterol in mmol/l	5 63±1 34	5 36±1 09
HDL-cholesterol in mmol/l (mean, S D)	1 29±0 39	1 41±0 35
Triglyceride in mmol/l (mean, S D)	2 08±1 10	1 50±0 93
LDL-cholesterol in mmol/l (mean, S D)	3 41±1 36	3 28±0 96
Cholesterol/HDL-cholesterol ratio (mean, S D)	4 95±2 93	4 12±2 35
CRP in mg/l (median, quartiles)	3 91 (1 6–10 0)	1 40 (0 5–5 1)

* Positive history of hypercholesterolemia was defined as the use of lipid lowering medication and/or cholesterol plasma concentration ≧ 5 0 mmol/l
† Positive history of diabetes was defined as the use of blood glucose lowering medication and/or (non-fasting) glucose plasma concentration ≧ 11 0 mmol/l
‡ Positive history of hypertension was defined as the use of antihypertensiva and/or systolic BP ≧ 160 mmHg and/or diastolic BP ≧ 90 mmHg

Table 2
Percentage positive IgG antibody titre for *C pneumoniae*, *H pylori* and CMV in PAD patients and control women

	PAD patients	Control women
*C pneumoniae**	23% (52/228)	13% (85/632)
H pylori†	40% (91/228)	26% (163/631)
CMV‡	71% (161/228)	56% (353/630)

* A positive *C pneumoniae* IgG titre is defined by an in-house enzyme-linked immunosorbent assay (ELISA) with cut-off titre chosen at 1 6400
† A positive *H pylori* IgG titre was defined by a commercial ELISA assay (Enzygnost®Anti-*H pylori* II/IgG, Dade Behring)
‡ A positive CMV IgG titre was defined by a commercial ELISA assay (Enzygnost® Anti-CMV/IgG, Dade Behring)

Table 3
Crude and adjusted odds ratios (95% CI) for *C pneumoniae*, *H pylori* or CMV and peripheral arterial disease

Adjustment	Infection		
	C pneumoniae	*H pylori*	CMV
No	1 9 (1 3–2 8)	1 9 (1 4–2 6)	1 9 (1 4–2 6)
Age	1 9 (1 3–2 9)	1 7 (1 2–2 3)	1 7 (1 2–2 4)
Age, smoking	2 0 (1 3–3 0)	1 7 (1 2–2 4)	1 7 (1 2–2 5)
Age, smoking, education	2 0 (1 3–3 1)	1 6 (1 1–2 2)	1 6 (1 1–2 3)

2 6) for CMV. After adjustment for potential confounders, the odds ratio was 2.0 (95% CI; 1.3–3.1) for *C pneumoniae,* 1 6 (95% CI; 1.1–2.2) for *H pylori* and 1.6 (95% CI; 1.1–2.3) for CMV. Attenuations of the odds ratios were mainly caused by adjustment for age.

The adjusted odds ratio for PAD increased with the cumulative number of infections and was 1 5 (95% CI, 1.0–2 4), 2.7 (95% CI; 1.6–4.4) and 3.5 (95% CI; 1.5–8.1) for women with one, two or three infections, respectively (Table 4). No positive relation between the number of infections and the CRP level was found. In healthy individuals with zero, one, two or three infections the median CRP levels were 1.6, 1.3, 1.3 and 1.5 mg/l, respectively (Kruskal–Wallis test, $P = 0.69$) and in PAD patients the median CRP levels were 4 3, 3.8, 3.6 and 7.6 mg/l, respectively (Kruskal–Wallis test, $P = 0.16$)

Analyses of subgroups according to CRP level showed that, among women with a high CRP level, the odds ratio for PAD also increased with the number of infections and was 3 0 (95% CI; 1.3–6.7) for one, 5.0 (95% CI; 0.1–11.9) for two and 7.6 (95% CI; 2.3–25 6) for three positive titres However, among women with a low CRP level, no significant increases of the odds ratios were observed, 1.3 (95% CI; 0.5–3 0), 1.5 (95% CI; 0.6–4 0) and 0.5 (95% CI; 0.1–4.8) for one, two or three infections, respectively (Table 5).

4. Discussion

Our data indicate that women with evidence of infection with *C pneumoniae, H pylori* or CMV have an increased risk of PAD. Age is a confounding factor in the relation between *H. pylori* infection and PAD, as well as in the relation between CMV and PAD The odds ratios slightly attenuate after adjustment for the

Table 4
Crude and adjusted odds ratios (95% CI) for the number of infections and peripheral arterial disease

	Number of infections			
	Zero ($n = 239$)	One* ($n = 365$)	Two† ($n = 222$)	Three‡ ($n = 32$)
No	1	1 7 (1 1–2 5)	3 2 (2 1–4 9)	4 5 (2 1–9 8)
Age	1	1 5 (1 0–2 3)	2 7 (1 7–4 2)	3 7 (1 7–8 1)
Age, smoking	1	1 6 (1 0–2 5)	2 9 (1 8–4 7)	3 6 (1 6–8 4)
Age, smoking, education	1	1 5 (1 0–2 4)	2 7 (1 6–4 4)	3 5 (1 5–8 1)

* Infection with *C pneumoniae* or *H pylori* or CMV
† A combination of two infections (*C pneumoniae* and *H pylori* or *C pneumoniae* and CMV or *H pylori* and CMV)
‡ A combination of three infections (*C pneumoniae*, *H pylori* and CMV)

Table 5
The CRP level and the number of infections separate and combined effects on PAD

CRP level	Number of infections	Patients	Controls	OR (95% CI)*
Low	0	10	109	1
High	0	29	91	1 6 (0 6–4 3)
Low	1	30	163	1 3 (0 5–3 0)
High	1	59	112	3 0 (1 3–6 7)
Low	2	26	80	1 5 (0 6–4 0)
High	2	59	57	5 0 (2 1–11 9)
Low	3	1	9	0 5 (0 1–4 8)
High	3	14	8	7 6 (2 3–25 6)

* Adjusted for age, smoking, education, history of hypercholesterolemia, of diabetes and of hypertension and body mass index

small age difference between the PAD patients and the women controls. However, all three relations are independent from the potentially confounding factors, smoking and SES; after adjustment, the relations did not alter significantly. Odds ratios adjusted for the remaining vascular disease risk factors (viz. history of hypercholesterolemia, diabetes mellitus or hypertension, BMI and CRP concentration) are not shown in Table 3 because they were not considered as potentially confounding factors. Of course, it could be possible that infections are associated with one of these risk factors. Recently, it has been shown that current infections with *H. pylori* and *C. pneumoniae* are associated with an atherogenic lipid profile [16,17]. Still, in our opinion, these risk factors should not be considered as real confounders, but rather as 'intermediate variables' in the relation between infection and atherosclerosis. Nevertheless, if adjustment for all above mentioned vascular disease risk factors was applied, the risks of PAD associated with a *C. pneumoniae* infection or an infection with CMV did not significantly change and became 1.9 (95% CI; 1.2–3.1) and 1.6 (95% CI; 1.1–2.5), respectively, whereas the risk related to *H. pylori* infection did decrease significantly (1.3 (95% CI; 0.9–2.0)).

Most (cross-sectional) case-control studies that have recently been published did show positive relations between IgG antibody titres against *C. pneumoniae, H. pylori* or CMV and CAD [18–23]. In contrast, most prospective studies did not show positive relations between the IgG antibody titres to the three infectious agents and CAD [24–33]. Studies that are cross-sectional in nature, such as the present investigation, cannot establish causality but can only show associations. Prospective studies, on the other hand, have the advantage of investigating temporal relationships, which makes it possible to differentiate between cause and effect. However, if the causal (exposure) variable varies over time or if the variable has its causal effect within a relatively short period of time (less than the follow-up period), misclassification of the exposure variable might occur to a larger extent in prospective studies compared to cross-sectional studies. Therefore, the results from a prospective study might be an underestimation of a real causal relation. One might argue that the apparent inconsistency of the results from prospective and cross-sectional studies on the relation between infection and CAD could be interpreted as a lack of a causal role of infections in atherogenesis. However, we argue that because of the applied prospective designs, the results that were found might be an underestimation of a real causal relation. In view of this, it becomes clear that the timing of the measurement of the antibody titres in relation to the onset of clinically recognised CAD needs to be carefully considered when interpreting the findings from sero-epidemiologic studies [34].

Our results show that 23% of the PAD patients and 13% (85/632) of the controls had a high positive IgG titre ($\geq$ 1:6400) against *C. pneumoniae*. The prevalence of detectable IgG antibodies against *C. pneumoniae* was much higher in both groups, 81 and 82% in patients and controls, respectively. The high cut-off titre (1:6400) that was used to calculate odds ratios has been defined prospectively and has frequently been used (in $\approx$ 50% of the publications) in other studies. If we had calculated the odds ratio for PAD in women who are sero-positive compared to women who are sero-negative, no significant relation between *C. pneumoniae* and PAD would have been found. Only a high positive titre ($\geq$ 1:6400) is significantly associated with PAD. This might indicate that the relation between *C. pneumoniae* and athero-

sclerosis might be due to chronic or repeated infections or might only be present in individuals with an enhanced humoral immune response to antigen presentation.

Since the cases in our study were collected within the 10-year-period (1990–1999) before determination of the antibody titres, it could be possible that cases were infected after they were diagnosed with PAD. However, no significant declining linear relations were found between the year of diagnosis and the percentages of the cases that were seropositive to each of the micro-organisms (data not shown). This argues against the possibility that PAD patients are more easily infected then healthy controls and therefore it pleads for a causal relation between infections and PAD.

The role of sero-epidemiology studies in determining the relationship between infection and atherothrombotic diseases, has been discussed in a recently published report of 'The Workshop Group on Epidemiology' [35]. There is a concern that population subsets of particular interest have not been dealt with in past epidemiology studies; most studies have been carried out in middle-aged and older male populations. Therefore, future studies should be extended to additional populations, such as women and young adults. The selection of young patients has the advantage that survival bias is reduced. Moreover, since the prevalence of seropositivity in a population increases with age, the relation between antibody titres and atherogenesis could be more obvious in a young population because younger PAD patients might contrast more strongly with age-matched controls than older patients.

Recently, it has been shown that the dominant mechanisms by which infections contribute to atherogenesis, are sex-determined (in the cited study the investigators have concentrated on CMV) [36].

In men, CMV was not independently associated with CAD, but CMV was associated with the CRP level and the CRP level was associated with CAD. In women, however, CMV was independently associated with CAD and did not significantly relate to the CRP level. The authors of the cited article state that, in men, if CMV contributes to CAD, it would appear to do so insofar as it predisposes to inflammation, whereas in women, CMV is an independent risk factor for CAD. The results of our study are in agreement with these earlier findings with regard to the independent relations that were found between CMV and the other pathogens and atherosclerosis in women. However, although we also did not find a significant association between the different infections and the CRP level (data not shown), we found that the relation between the infection burden and PAD is stronger in women with a high CRP level compared to women with a low CRP level. This indicates that, in women, as in men, inflammation plays a part in atherogenesis.

Of the 905 women controls who were approached to participate in this study, 262 could not be reached or refused to participate. Of the 270 PAD patients who were successfully approached, 228 (78%) agreed to participate and 43 could not be included. To test for potential selection bias in our study, we compared the group of individuals who were included with those who refused to participate. The distribution of vascular risk factors, such as hypertension, hypercholesterolemia, diabetes and smoking, did not differ between the not included and the included individuals.

According to our data, the risk of PAD seems not only related to a single pathogen in particular, but also to the cumulative number of pathogens to which an individual has been exposed. Similar results were found in (nested) case-control studies on the association between the number of infections and CAD [37–41]. However, another, recently published, prospective study indicated that infection burden was not a risk factor for future cardiovascular events [26]. It is noteworthy that this prospective study also did not show a positive relation between each separate infectious agent and CAD. The role of pathogen burden, together with possible mechanisms that link infections with atherosclerosis, has been discussed earlier [42]. Beside the proatherosclerotic effects of direct infection of cells of the vessel wall, distant infections might also induce changes in the vessel wall that contribute to atherogenesis. Firstly, these changes could be mediated through alterations caused by circulating cytokines induced by the infection of distant tissues. Secondly, molecular mimicry—a mechanism requiring that the infecting pathogen contains peptides homologous to those present in host proteins—could result in an immune response that, although it was stimulated by and targeted to pathogen antigens, also attacks host tissues that contain the cross-reacting peptides. This pathogen-induced mechanism does not require the presence of a pathogen in the target tissue and there are many possible homologous pathogen/host peptides that could cause the auto-immunity targeted to the arterial walls. Both last mentioned mechanisms explain that a variety of pathogens and that pathogen burden are able to affect the arterial wall in an indirect way.

In our data, we have found a positive relation between the pathogen burden and PAD, exclusively in the subgroup of women with a high CRP level. This suggests that an inflammatory response might indeed be involved in the process that relates infections with PAD. It appears that reactivity of the inflammatory system is a necessary factor for chronic infections to have a role in atherogenesis.

In summary, the present study demonstrates that infections with *C. pneumoniae*, *H. pylori* and CMV are related to PAD in approximately the same extent as they are related to CAD. Moreover, that the risk of PAD is

not only related to a certain pathogen in particular, but also to the cumulative number of infections In our data, we found that the positive relation between the pathogen burden and PAD was found exclusively in the subgroup of women with a high CRP level This suggests that an inflammatory response might indeed be involved in the process that relates infections with PAD It appears that reactivity of the inflammatory system is a necessary factor for chronic infections to have a role in atherogenesis

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