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Association between infectious burden, socioeconomic status, and ischemic stroke

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ABSTRACT

Background and aims: Infectious diseases contribute to stroke risk, and are associated with socioeconomic status (SES). We tested the hypotheses that the aggregate burden of infections increases the risk of ischemic stroke (IS) and partly explains the association between low SES and ischemic stroke.
Methods: In a case–control study with 470 ischemic stroke patients and 809 age- and sex-matched controls, randomly selected from the population, antibodies against the periodontal microbial agents *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*, against *Chlamydia pneumonia*, *Mycoplasma pneumoniae* (IgA and IgG), and CagA-positive *Helicobacter pylori* (IgG) were assessed.
Results: IgA seropositivity to two microbial agents was significantly associated with IS after adjustment for SES (OR 1.45 95% CI 1.01–2.08), but not in the fully adjusted model (OR 1.32 95% CI 0.86–2.02). By trend, cumulative IgA seropositivity was associated with stroke due to large vessel disease (LVD) after full adjustment (OR 1.88, 95% CI 0.96–3.69). Disadvantageous childhood SES was associated with higher cumulative seropositivity in univariable analyses, however, its strong impact on stroke risk was not influenced by seroepidemiological data in the multivariable model. The strong association between adulthood SES and stroke was rendered nonsignificant when factors of dental care were adjusted for.
Conclusions: Infectious burden assessed with five microbial agents did not independently contribute to ischemic stroke consistently, but may contribute to stroke due to LVD. High infectious burden may not explain the association between childhood SES and stroke risk. Lifestyle factors that include dental negligence may contribute to the association between disadvantageous adulthood SES and stroke.

1. Introduction

Stroke, especially ischemic stroke (IS), is a multifactorial disease with numerous contributing risk factors. These risk factors are target of preventive strategies attempting to mitigate the future burden of stroke. Current risk factor models may explain about 90% of ischemic stroke occurrence [1]. However, some epidemiological aspects of stroke may not be sufficiently explained yet [2–4].

Infectious and inflammatory diseases, as well as unfavorable socioeconomic conditions have been described as contributors to the risk of stroke [4–7]. Different chronic infections have been found to be associated with stroke, including clinical periodontitis, infections with the periodontal pathogens *Porphyromonas gingivalis* (Pg) and *Aggregatibacter actinomycetemcomitans* (Aa), infections with *Helicobacter pylori* (Hp), and particularly with *Hp* strains carrying the cytotoxin-associated gene A (CagA) [8–11]. *Chlamydia pneumonia* (Cp), *Mycoplasma pneumonia* (Mp), and *Legionella pneumophila* (Lp) are as well among those microbial agents whose link with stroke has been discussed [12]. However, the results of

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studies investigating single agents are ambiguous [13]. A current hypothesis suggests that the aggregate burden of microbial agents to which an individual has been exposed to during his or her whole lifetime, rather than single pathogens, increases the risk of stroke ("infectious burden concept") [5]. In a recent analysis of the Northern Manhattan Study, no association was found between the risk of stroke and any of the five serologies to common infections (Cp, Hp, Cytomegalovirus, Herpes Simplex Virus 1 and 2). However, a derived infectious burden index showed an association with stroke [14].

Socioeconomic status (SES) is negatively associated with the risk of stroke [15]. In a case-control study, we recently showed that SES during childhood and adulthood are each independently linked to stroke risk [16]. Several chronic infectious diseases such as periodontitis and infection with *Hp* are more common in people with disadvantageous social conditions [17]. Thus, it seems likely that chronic infections contribute to the association between socioeconomic conditions and stroke, together with other factors such as a health neglecting lifestyle.

Based on the data from the same case-control study, we tested the hypotheses that the infectious burden (=aggregate number of seropositivities to selected infectious agents) is associated with the risk of IS and that chronic infections and elements of a health neglecting lifestyle contribute to the association between SES during childhood, adolescence, and adulthood and the risk of IS.

2. Patients and methods

The "GENESIS" study is a case-control study with 470 first-ever ischemic stroke (FEIS) cases (40% women, mean age 66.5 ± 10.8 years; 60% men, 65.5 ± 10.7) and 809 age- and sex-matched controls (41.8% women, 66.4 ± 11.1; 58.2% men, 67.9 ± 9.5), randomly selected from the general population. The target population consists of individuals aged 18–80 years, living in the city of Ludwigshafen am Rhein in South-West Germany. „GENESIS" was established within the framework of the Ludwigshafen Stroke Study (LuSST), a population-based stroke registry that started on January 1st, 2006, using standard definitions and multiple overlapping methods of case-ascertainment in order to identify all cases with incident stroke or transient ischemic attack among the population of Ludwigshafen (163.340 inhabitants on December 31, 2009). A detailed description of LuSSt and the „GENESIS" study have been published recently [16,18]. The study was approved by the ethics committee of the Landesärztekammer Rheinland-Pfalz (837.333.05(4991)).

2.1. Inclusion and exclusion criteria

Inclusion criteria besides age and permanent residency in the study area were Caucasian ethnicity and written informed consent to study participation. Inclusion criterion for cases was the diagnosis of a FEIS based on an acute neurological deficit lasting >24 h with no other reason than cerebral ischemia. All cases received a cerebral CT or MRI. Exclusion criteria for both cases and controls included any previous stroke, myocardial infarction within 90 days, dementia, severe aphasia, insufficient understanding of the German language or any other relevant communication barrier and severe disability that precludes interview participation.

2.2. Recruitment

For recruitment of controls, a random sample of Ludwigshafen residents was drawn from the population registry including name, age, sex and address. Subsamples were consecutively taken to match the age and sex distribution of cases. Those selected received invitation letters with detailed information on the study and request for their participation. The participation rate for controls was 46.6%. The cases included incident stroke cases from the LuSSt registry. According to the study protocol only in-patients at the Klinikum Ludwigshafen were asked for participation in "GENESIS", since only few patients in the area did not attend this hospital. This group represents about 89% of all cases in LuSSt. The participation rate for cases was 73.7%.

2.3. Data collection and laboratory tests

Cases and controls were interviewed by trained interviewers using a standardized questionnaire. We collected data on age, sex, anthropometric measures, previous diseases, and previous visits to a dentist as markers of health behavior, number of teeth, smoking, alcohol intake, physical activity, dietary patterns, medication and social history. In both, cases and controls, blood pressure was measured after 5 min of resting, a 12-lead electrocardiogram and a Duplex-sonography of brain supplying arteries were performed. Venous blood samples were taken in cases and controls.

Serum was separated by low-speed centrifugation and stored at −70 °C until analysis. Serum levels of IgA and IgG antibodies against *Aa* and *Pg* were determined by multi-serotype-ELISA as previously described [19]. Serum levels of IgG antibodies against *Hp* and of IgG and IgA antibodies against *Cp* and *Mp* were assessed by using commercial enzyme immunoassays (Enzygnost® and Novagnost® Siemens Healthcare) at the Institute of Clinical Chemistry, Klinikum Ludwigshafen.

2.4. Definition of variables

Cardiovascular risk factors were defined according to current national and international guidelines and have been described in detail [20]. A detailed presentation of the SES measures has been published recently [16]. Etiological subtypes of IS were ascertained using modified TOAST criteria (Trial of ORG 10172 in Acute Stroke Treatment) as previously described [20]. The category "large vessel disease" (LVD) included "probable atherothrombotic stroke" (AT) and stroke due to "large artery atherosclerosis" (LAA). In 159 cases, etiology of IS was classified as LVD (19.7% of all cases).

2.5. Statistical analysis

We report absolute and relative frequencies of risk factors, SES and seropositivities to infectious agents by case–control status. Infectious burden was calculated as cumulative IgA-positivity, cumulative IgG-positivity, and aggregated IgG/IgA-positivity. Odds ratio (OR) estimates and 95% confidence intervals (CI) are presented based on conditional logistic regression models, conditioned on age (2-year-age groups) and sex, and adjusted for risk factors, SES, and the respective other infection indicators. Associations between the number of seropositivities to infectious agents and SES in childhood, adolescence, and adulthood were investigated by the Jonckheere-Terpstra trend test. To control for a potential bias owing to a lower response of controls from more disadvantaged social background, we performed a sensitivity analysis, comparing school education data in our control group with those of the general population received from the municipal statistical office. Although individuals with low school education were moderately underrepresented in our control group, results regarding socioeconomic factors as stroke risk factor were altered only to a minor degree by adjustment for a differential response rate in controls [16]. For all analyses, the statistical software R was used, conditional logistic regression estimates were obtained through the R package survival, the Jonckheere-Terpstra trend test

from the R package clinfun [21–23].

3. Results

Distribution of traditional risk factors, lifestyle risk factors, socioeconomic risk score and dental risk factors in cases and controls is shown as a supplementary table as previously published [16]. FEIS cases showed higher rates of seropositivity regarding IgA antibodies against *Aa* and IgG antibodies against CagA-positive strains of *Hp* but lower rate of seropositivity to IgG antibodies against *Mp* in analyses adjusted for age and sex only. Cumulative IgA-seropositivity against 2 bacterial strains was associated with higher stroke risk, but cumulative IgG or combined IgA/IgG seropositivity was not (Table 1).

Adjustment for SES in childhood, adolescence and adulthood and further adjustment for cardiovascular risk factors and dental parameters had mostly small effects on the risk estimates of the immunological variables (Fig. 1A). The association between *Hp* and IS was weakened and rendered nonsignificant by adjustment for SES. IgA seropositivity to two microbial agents was significantly associated with IS after adjustment for SES (OR 1.45 95% CI 1.01–2.08). Fully adjustment rendered effect of IgA-seropositivity to two microbial agents on stroke risk nonsignificant (OR 1.32 95% CI 0.86–2.02).

Distribution of risk factors and data on SES was reported previously [16]. Data on dental health showed that patients suffered more often from advanced tooth loss (8–14 teeth remaining) and used dental health care service less than controls (Table 2).

When analyzing cases with LVD separately, IgA-seropositivity for *Aa* (OR 1.68; 95% CI 1.15–2.46) and *Cp* (OR 1.89; 95% CI 1.14–3.13), cumulative IgA-seropositivity for 2 (OR 2.14; 95% CI 1.28–3.56) and 3–4 microbial agents (OR 2.50; 95% CI 1.11–5.65), and IgG-seropositivity for *Hp* (OR 1.63; 95% CI 1.14–2.34) were associated with stroke in age- and sex-adjusted analyses (Fig. 1B; Table 3). Adjustment for SES and further adjustment for cardiovascular risk factors only marginally changed the effect estimates for most seroepidemiological analyses including IgA against *Aa*. The association for *Cp* IgA and *Hp* IgG was weakened and rendered nonsignificant as was the cumulative IgA-seropositivity (two agents: OR 1.88, 95% CI 0.96–3.69; 3–4 agents: OR 1.58 95% CI 0.51–4.89). *Cp*-IgG-seropositivity was associated with higher risk of stroke due to small vessel disease SVD (OR 1.53; 95% CI 1.04–2.25), an effect that was not found after further adjustment (OR 1.12; 95% CI 0.67–1.86).

In unadjusted analyses, poor SES in childhood was associated with higher numbers of seropositivities to infectious agents in controls ($p = 0.02$; Jonckhere-test), but particularly in cases ($p = 0.0001$) (Fig. 2). This association was detected for SES in adolescence for cases as well ($p = 0.03$), but not for controls ($p = 0.2$) and did not exist in either group regarding adulthood (cases: $p = 0.1$; controls: $p = 0.6$).

Adjusting for infectious burden had no notable influence on the association between of the risk of stroke and SES in childhood, adolescence, or adulthood (Table 2, model 2). The link between SES in adulthood and stroke risk was reduced and rendered nonsignificant when dental status and frequency of dental health care were additionally adjusted for (Table 2, model 3).

Table 1
Distribution, odds ratios and 95%-confidence intervals of serological testing and aggregate number of seropositivities to infectious agents for all ischemic stroke cases.

	Controls	%	Cases	%	Crude OR[a]	95% CI
Mycoplasma pneumonia						
IgA	24	2.98	15	3.22	1.04	0.53–2.06
IgG	445	55.28	232	49.79	0.74	0.59–0.95
Porphyromonas gingivalis						
IgA	434	53.91	253	54.88	1.06	0.83–1.35
IgG	594	73.79	344	74.62	1.08	0.81–1.42
A. actinomycemtemcomitans						
IgA	220	27.33	146	31.67	1.33	1.02–1.73
IgG	244	30.31	118	25.60	0.86	0.66–1.13
Chlamydia pneumonia						
IgA	73	9.07	53	11.37	1.28	0.86–1.90
IgG	235	29.19	145	31.12	1.08	0.83–1.40
Helicobacter pylori						
IgG	243	30.19	182	39.06	1.39	1.08–1.78
Cumulative IgA positivity						
0	264	32.88	142	30.80	1.00	
1	364	45.33	189	41.00	1.00	0.75–1.33
2	142	17.68	112	24.30	1.47	1.05–2.08
3–4	33	4.11	18	3.90	1.25	0.66–2.36
Cumulative IgG positivity						
0–1	220	27.40	125	27.11	1.00	
2	271	33.75	160	34.71	1.09	0.80–1.48
3	227	28.27	109	23.64	0.86	0.62–1.20
4–5	85	10.59	67	14.53	1.29	0.85–1.95
Cumulative overall positivity						
0–1	184	22.91	103	22.34	1.00	
2	264	32.88	148	32.10	1.03	0.74–1.43
3	235	29.27	120	26.03	0.94	0.67–1.33
4–5	120	14.94	90	19.52	1.29	0.88–1.90

Few data missing: in controls: Mp, Pg, Aa, Cp, Hp: n = 4; in cases: Mp, Cp: 4; Pg, Aa:n = 9.
[a] Conditioned on age (2-year-groups) and sex.

4. Discussion

Using a large age- and sex-matched case-control study including detailed data on SES, we found that *Aa*-IgA antibody levels were positively, and *Mp*-IgG antibody levels were negatively associated with FEIS independent of conventional risk factors and SES. The increased risk found for *Aa* was mainly due to an association with stroke due to LVD, whose main contributor is atherosclerosis, whereas the inverse association found for *Mp* was not significantly linked to any stroke subtype. The other three microbial agents studied (*Cp*, *Hp* and *Pg*) were not independently associated with the overall stroke risk. Cumulative IgA seropositivity was associated with higher risk of FEIS in univariable analysis and after adjustment for SES, but not in the fully adjusted model.

Several serological studies have suggested single chronic infections, as well as the burden composed of several chronic infections as risk factors for stroke [24,25]. The research has mainly focused on *H. pylori*, Cytomegalovirus, Herpes simplex virus, periodontal pathogens, or their combinations [9,10,12,14,26–29]. We investigated the five selected microbes for the following reasons: there is ample evidence that periodontitis increases the risk of stroke and *Aa* and *Pg* are among the most relevant periodontal agents [30]. We had previously shown that in our region CagA positive *Hp* strains are linked to stroke risk albeit results e.g. from Asia are at variance [11,31]. In addition, we selected *Cp* and *Mp* among respiratory agents as particularly *Cp* previously was in the focus of research.

Pg and *Aa* have different characteristics and virulence profiles, but they are both considered to be etiologically linked to periodontitis, which is the sixth most common medical condition according to the Global Burden of Disease Study [32]. *Pg* is very frequent in chronic adult periodontitis, whereas *Aa* is recurrently encountered in a more aggressive form of the disease, often already starting in adolescence. Both pathogens, however, are very common in adults: according to a Finnish population-based study *Pg* and *Aa* are found in 35.5% and 20.0% of saliva samples, respectively [33]. In the present study, only *Aa* was associated with increased stroke risk, which is in agreement with an earlier prospective study

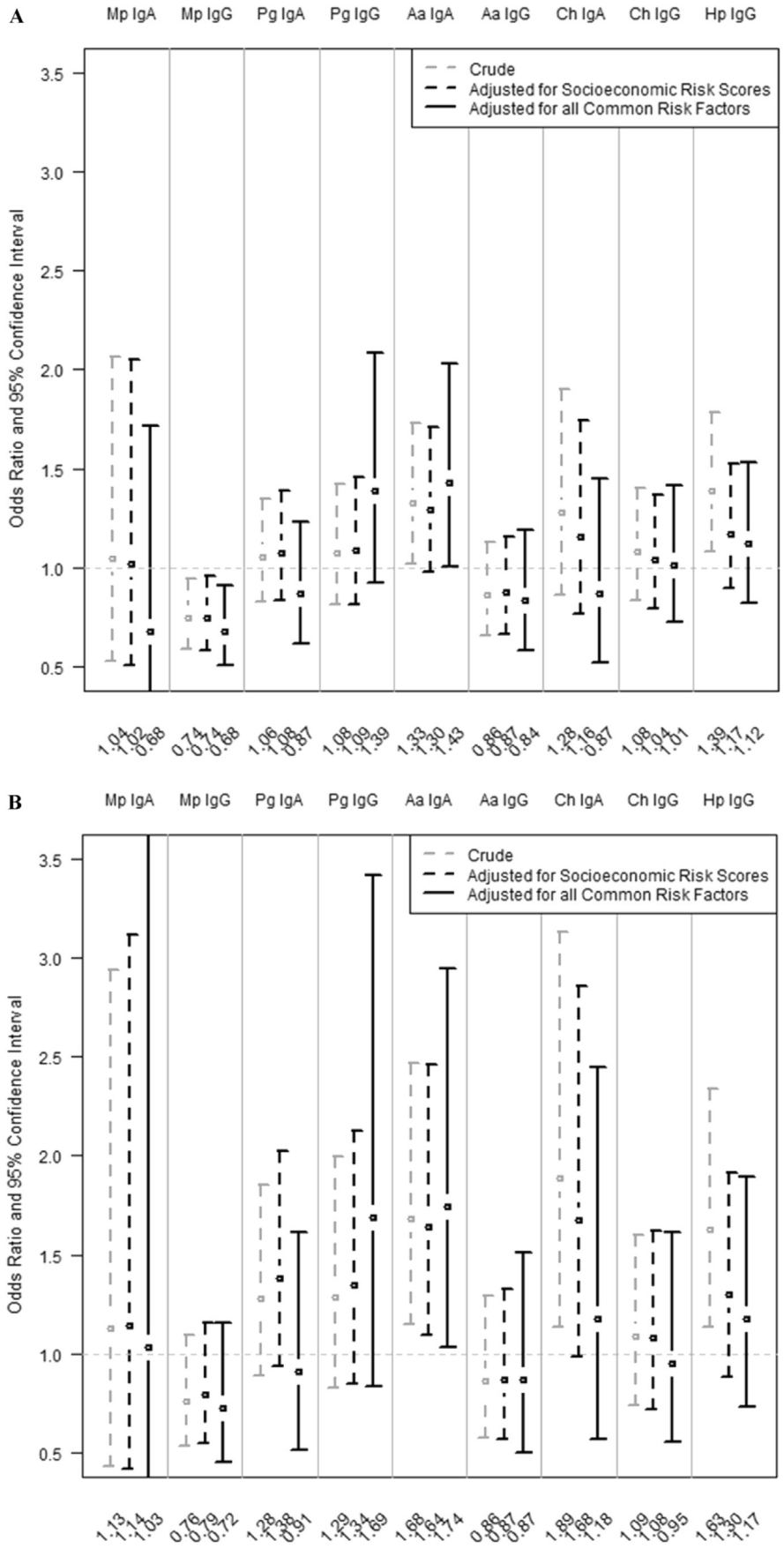

Fig. 1. Odds ratios and 95%-confidence intervals of ischemic stroke by serology of chronic infections in three different models: (1) conditioned on age and sex, (2) additionally adjusted for socioeconomic risk scores in childhood, adolescence and adulthood, and (3) additionally for all common known risk factors (hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation, smoking, (high) alcohol consumption, physical activity, fruit or vegetable consumption, meat consumption, number of teeth, number of dentist visit). (A) Ischemic stroke overall, (B) ischemic stroke due to large vessel disease.

Table 2
Odds ratios and 95%-confidence intervals in three multivariable models, for all ischemic stroke cases.

	Model 1		Model 2		Model 3	
	OR	95% CI	OR	95% CI	OR	95% CI
Risk score childhood						
Low	1		1		1	
Middle	1.47	1.04–2.09	1.42	1.0–2.02	1.46	1.02–2.09
High	1.77	1.20–2.60	1.72	1.16–2.55	1.68	1.11–2.52
Risk score adolescence						
Low	1		1		1	
Middle	1.28	0.90–1.82	1.26	0.89–1.80	1.31	0.91–1.88
High	1.64	0.97–2.78	1.64	0.96–2.79	1.62	0.93–2.82
Risk score adulthood						
Low						
Middle	0.89	0.62–1.29	0.90	0.62–1.31	0.82	0.56–1.20
High	1.74	1.16–2.60	1.73	1.15–2.59	1.47	0.97–2.23
Cumulative IgA positivity						
0			1		1	
1			1.00	0.72–1.40	1.03	0.73–1.45
2			1.30	0.86–1.96	1.32	0.86–2.02
3–4			0.89	0.41–1.94	0.77	0.33–1.78
Cumulative IgG positivity						
0–1			1		1	
2			1.02	0.71–1.47	1.09	0.75–1.59
3			0.87	0.59–1.30	0.92	0.61–1.38
4–5			0.93	0.56–1.54	1.02	0.61–1.70
No. of teeth						
22–28					1	
15–21					0.87	0.55–1.38
8–14					2.33	1.41–3.85
0–7					1.07	0.75–1.53
Dentist visits						
>1× per year					1	
1× per year					0.94	0.69–1.29
<1× per year					1.32	0.79–2.19
Never					4.47	2.41–8.28

In addition to the depicted parameters all models include age (2-year-groups) sex, hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation, coronary heart disease, chronic heart failure, peripheral arterial disease, current smoking, high alcohol consumption, physical activity, fruit/vegetable consumption, meat consumption as published in Ref. [16].

on stroke incidence [9]. In another study, *Aa* leukotoxin neutralizing antibodies have been associated with decreased risk of stroke further supporting a relevant role of this microbe and its virulence factors in cerebrovascular diseases [34]. Seropositivity to *Aa* does not necessarily denote current periodontitis, but it reflects presence of the pathogen in oral biofilm and the antibody levels are strongly correlated with oral bacterial load [35]. In periodontitis, serum IgA-class antibodies to the pathogen are considered to reflect repeated exposure, which occurs during daily dental routines through bleeding and infected gums. Recurrent bacteraemia, endotoxemia, and spread of antigens lead to low-grade systemic inflammation regardless of the bacterial source [36].

Mp-seropositivity was found to be associated with the risk of stroke and coronary events in several studies, whereas other studies' results were negative [37,38]. Our study is the first one showing a negative association, which however might be a spurious result.

Our study did not confirm the hypothesis of significant associations between infectious burden measured with cumulative IgA-serology, IgG-serology, or aggregated IgG/IgA-positivity to five chronic pathogens, and the overall risk of IS. Heterogeneity of IS etiology might partly explain the study results. Atherosclerosis is thought to play a key role in mechanisms linking chronic infections and IS [14,39]. In stroke etiology, atherosclerosis is the main contributor to stroke of LVD origin. Our study showed an association between cumulative IgA-seropositivity and IS in the LVD subgroup, however, this association was weakened after adjustment for all covariates.

We found that disadvantageous childhood socioeconomic conditions reflect increased risk of stroke independent of SES in later life stages and independent of conventional risk factors, including smoking, alcohol consumption, diet and physical activity [16]. The etiology of this association is hardly understood. We had hypothesized that high infectious burden may partly explain this correlation as low SES in childhood increases the risk of infectious diseases including chronic persistent infection with microbial

Table 3
Distribution, odds ratios and 95%-confidence intervals of serological testing and aggregate number of seropositivities to infectious agents, by TOAST-subgroups.

	LVD	%	Crude OR[a]	95% CI	CE	%	Crude OR[a]	95% CI	SVD	%	Crude OR[a]	95% CI
Mycoplasma pneumonia												
IgA	6	3.75	1.13	0.43–2.94	6	5.61	2.11	0.80–5.58	3	2.11	0.73	0.21–2.55
IgG	83	51.88	0.76	0.53–1.09	48	44.86	0.73	0.48–1.11	70	49.30	0.75	0.52–1.08
Porphyromonas gingivalis												
IgA	97	60.62	1.28	0.89–1.85	59	55.14	1	0.65–1.54	69	48.59	0.87	0.60–1.27
IgG	126	78.75	1.29	0.83–2.00	73	68.22	0.82	0.50–1.33	104	73.24	1.10	0.71–1.69
Aggregatibacter actinomycem												
IgA	59	36.88	1.68	1.15–2.46	34	31.78	1.29	0.81–2.04	38	26.76	1.05	0.68–1.60
IgG	41	25.62	0.86	0.58–1.29	30	28.04	1.04	0.65–1.66	32	22.54	0.72	0.46–1.11
Chlamydia pneumonia												
IgA	26	16.25	1.89	1.14–3.13	8	7.48	0.82	0.38–1.80	13	9.15	0.99	0.52–1.89
IgG	52	32.5	1.09	0.74–1.60	26	24.3	0.85	0.52–1.38	54	38.03	1.53	1.04–2.25
Helicobacter pylorii												
IgG	71	44.38	1.63	1.14–2.34	41	38.32	1.30	0.84–2.01	49	34.51	1.18	0.79–1.74
Cumulative IgA positivity												
0	38	23.75	1		29	27.10	1		54	38.03	1	
1	64	40	1.31	0.83–2.07	43	40.19	0.94	0.56–1.59	54	38.03	0.75	0.49–1.15
2	47	29.38	2.14	1.28–3.56	29	27.10	1.58	0.87–2.86	27	19.01	0.93	0.54–1.58
3–4	10	6.25	2.5	1.11–5.65	2	1.87	0.56	0.12–2.55	5	3.52	0.95	0.34–2.66
Cumulative IgG positivity												
0-1	35	21.88	1		33	30.84	1		38	26.76	1	
2	57	35.62	1.23	0.77–1.98	33	30.84	0.86	0.50–1.46	47	33.10	1.09	0.67–1.75
3	39	24.38	0.98	0.59–1.64	22	20.56	0.66	0.36–1.19	39	27.46	1.07	0.65–1.76
4–5	28	17.5	1.66	0.91–3.01	15	14.02	1.22	0.60–2.46	16	11.27	1.04	0.53–2.04
Cumulative overall positivity												
0-1	28	17.5	1		26	24.3	1		34	23.94	1	
2	48	30	1.08	0.64–1.81	36	33.64	0.97	0.55–1.70	43	30.28	0.96	0.58–1.59
3	42	26.25	1.08	0.63–1.85	24	22.43	0.73	0.40–1.35	41	28.87	1.01	0.61–1.69
4–5	41	25.62	1.83	1.04–3.22	17	15.89	0.95	0.47–1.90	22	15.49	1	0.54–1.86

[a] Conditioned on age (2-year-groups) and sex.

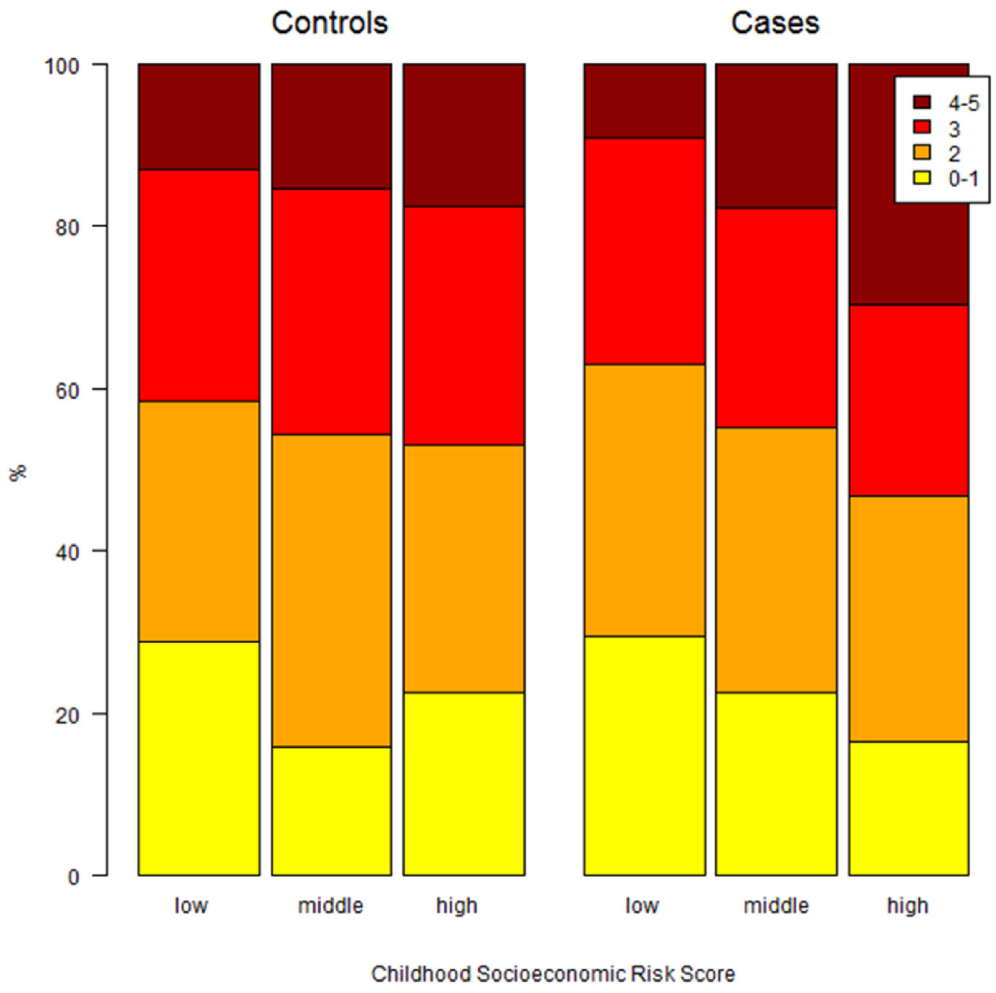

Fig. 2. Socioeconomic risk score in childhood by combined IgA/IgG seropositivity.

agents such as *Hp* [17]. In fact we found a strong correlation between aggregate burden of infections and SES in childhood in cases, and to a weaker degree in adolescence. In controls, such association was less pronounced but significant in childhood and not existent in adolescence. These findings are in line with previous results. However, addition of serological data only slightly attenuated the effect of childhood socioeconomic status on stroke. Thus, the effect of presently examined infections on the association between childhood SES and IS is low.

Interestingly, advanced tooth loss (8–14 remaining teeth) and avoidance of dental health care service were strongly and independently associated with FEIS. Inclusion of the number of teeth and the frequency of dentist visits reduced the strength of the association between low SES in adulthood and stroke, and rendered it nonsignificant. This indicates that behavioral and other factors that are reflected by dental care or the sequelae of dental negligence contribute to the link between SES and stroke, a finding that has not been reported so far to the best of our knowledge. Of note, periodontitis, a chronic infectious disease that is influenced by several behavioral (e.g. smoking) and socioeconomic factors, is among the most common contributors to the loss of teeth.

Our study has several limitations including the low number of microbial agents assessed, the low number of subjects in etiologic stroke subgroups a low response rate in controls and the fact that diagnosis of prior MI (>90 days) was not analyzed separately. In addition, the individual reason for missing teeth was unknown. Strengths of our study include the ample information on SES in different life periods and on other stroke risk factors.

In conclusion, we could not find that infectious burden as assessed with five microbial agents independently contributes to stroke risk in a consistent way. Low SES in childhood is associated with stroke risk and with a higher number of antimicrobial seropositivities. However, this elevated infectious burden does not contribute to our understanding of the link between childhood conditions and stroke. Advanced tooth loss due to dental negligence appears to be part of a lifestyle that contributes to the association between disadvantageous adulthood SES and FEIS.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2016.10.008.

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