Potential Association Between Bacterial Infections and Ischemic Stroke Based on Fifty Case-Control Studies: A Systematic Review and Meta-Analysis

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Research article

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Abstract

Background: Stroke is considered as one of the most concerns in health services facilities worldwide, and occurs in two types, ischemic stroke and hemorrhagic stroke. However, almost the three quarters of stroke cases are ischemic stroke which occur in effect of several risk factors such as hypertension, obesity, atherosclerosis, diabetes mellitus, arteritis, and inflammatory response. In recent years, infectious diseases are considered as one of the most important risk factors of ischemic stroke. In this regard, some bacteria causing the chronic infections in particular *Chlamydia pneumonia*, *Helicobacter pylori*, *Mycoplasma pneumonia*, and *Mycobacterium tuberculosis* get more attended.

Methods: In the present meta-analysis, we studied 50 case-control studies and evaluated potential relevance of these infections with creation and development of ischemic stroke.

Results: We surveyed the information of 33,978 participants in several nested case-control studies and demonstrated that bacterial infections can increase the risk of ischemic stroke.

Conclusions: In this meta-analysis we demonstrated a meaningful relationship between infection by three bacteria *C. pneumoniae*, *H. pylori*, and *M. tuberculosis* with occurrence of ischemic stroke.

1. Background

Nowadays stroke is accounted as one of the most striking complications of cardiovascular disorders, and is classified into the two groups, ischemic stroke and hemorrhagic stroke. The frequency of ischemic stroke is more that the hemorrhagic stroke, so that about 71% of strokes are ischemic and others are hemorrhagic (1). In general, strokes (ischemic and hemorrhagic) are known as the second most common cause of death in the world, and have affected 13.7 million worldwide (2). This disease is turn to one of the global health concerns, so that it is estimated that one out of four people would be experienced it during life (3). Several risk factors play a fundamental role in stroke occurrence which include obesity, hypertension, smoking, dyslipidemia, diabetes mellitus, alcohol consumption, atrial fibrillation, carotid stenosis, inflammation, and epigenetic events of host (4). Lately the role of inflammatory process in forming and promoting atherosclerotic plaques, carotid intima-media thickness (CIMT), arterial wall disruption, and vascular wall instability has been well documented (5). However, it is not well known the role of infectious agents as inflammatory response, but there are various documents regarding microorganisms such as Cytomegalovirus (CMV), Hepatitis C virus (HCV), Human immunodeficiency virus (HIV), Herpes simplex virus type 1–2 (HSV 1–2), Epstein Barr virus (EBV), Influenza virus, periodontal microflora, *Helicobacter pylori*, *Chlamydia pneumoniae*, *Haemophilus influenza*, *Mycoplasma pneumoniae*, *Mycobacterium tuberculosis*, *Streptococcus pneumonia*, *Tannerella forsythia*, and their role in formation of atherosclerotic lesions, metabolism disorders, hypertension, and promotion of cardiovascular disease (CVD) indexes (6–11). It seems that human pathogenic bacteria can be assumed as risk factors in developing CVD through mechanisms such as toxins, enzymes, influence on host immune response during chronic infections, and infective endocarditis (3, 6). According to review of the literature, endocarditis and septicemia increase the risk of infection to stroke (12); Nevertheless, information is limit in this context. The present study was done for the purpose of plausible relationship between ischemic stroke and infection by *H. pylori*, *C. pneumoniae*, *M. pneumoniae*, and *M. tuberculosis*. Also, potential risk for affecting to stroke was estimated for each group of infective agents.

2. Methods

2.1. Literature search strategy

The comprehensive systematic search up to May 2020 was used databases Scopus, PubMed, Cochrane Library, Embase, and Google scholar. For searching, we used keywords "*Helicobacter pylori*" AND "Ischemic Stroke" OR "*Chlamydia pneumonia*" AND "Ischemic Stroke" OR "*Mycoplasma pneumonia*" AND "Ischemic Stroke" OR "*Mycobacterium tuberculosis*" AND "Ischemic stroke" OR "Bacterial infection" AND "Ischemic stroke". Without limitation in date of publication, all published English article were retrieved. Searching strategy was done by two authors, separately; in disagreements, the third author judged and made decision.

2.2. Study selection criteria

In the present meta-analysis inclusion criteria were contained four items: 1) case-control studies on the role of bacterial infections in developing to ischemic stroke; 2) the only included studies on the role of infection by *H. pylori*, *C. pneumoniae*, *M. pneumoniae*, and *M. tuberculosis*; 3) accordance of methods based on standard protocols including ELISA and other immunoassays, conventional microbiology methods, PCR, blotting assay, and finally urease breath test; 4) clarity in the results of studies. In addition, the studies consist of case-report, letter to editor, review, congress abstract, non-English, prospective or cohort, and also other studies such post-stroke infections, repetitive results, and unclear studies, were considered as exclusion criteria. The flowchart of included studies is presented in Fig. 1.

2.3. Quality assessment and data collection

The quality assessment of included studies was evaluated by The Newcastle-Ottawa Scale (NOS). Required information include first author, publication year, location of each studies, type of infection agents, diagnostic methods for infection, age, gender, case group, control group, and number of infected cases in both case and control groups (Table 1).

Table 1
Characteristics of included studies

First Author	Year	Area	Age (year)		Gender (F/M)		Case group (n)	Control group (n)	Microorganism type	Number of bacterial infections (n)		Method
			case	control	case	control				case	control	
Masoud	2005	Iran	64.3	61.7	43/48	40/40	91	80	*H. pylori*	59	36	ELISA
Srivastava	2014	India	43.6	43.2	NA	NA	80	80	*C. pneumoniae*	42	26	ELISA
Muller	2003	Denmark	69	45	84/109	125/243	193	368	*C. pneumoniae*	20	29	PCR
Jozwiak	2007	Poland	44	40	40/54	44/59	94	103	*C. pneumoniae*	63	15	ELISA
Kongoji	2005	Japan	63.5	62.7	7/6	2/5	13	7	*C. pneumoniae*	5	0	PCR
Kawamoto	2003	Japan	75	74	17/23	48/37	40	85	*C. pneumoniae*	29	52	ELISA
Gabrielli	2003	Italy	68	66	56/49	66/64	105	130	*H. pylori*	75	81	ELISA
Sagar	2016	India	47.8	46.6	14/25	8/22	39	30	*H. pylori*	26	12	ELISA
Majka	2002	Germany	NA	NA	NA	NA	80	80	*H. pylori*	69	54	ELISA
Mrđen	2017	Croatia	72.8	72.8	34/32	34/32	82	93	*H. pylori*	21	32	ELISA
Ashtari	2008	Iran	65.4	60.2	43/38	24/19	81	43	*H. pylori*	57	29	ELISA
Lin	2008	Taiwan	64.2	63.2	202/248	198/252	450	450	*C. pneumoniae*	334	257	ELISA
Ponzetto	2002	Italy	56.7	57.4	22/58	88/232	80	320	*H. pylori*	64	190	UBT
Bandaru	2008	India	47.8	47.8	149/51	149/51	200	200	*C. pneumoniae*	72	35	ELISA
Mousavi	2011	Iran	65.6	62.9	46/50	36/57	96	93	*H. pylori*	44	39	ELISA
Hassanein	2014	Egypt	53	52.6	35/55	25/35	90	60	*H. pylori*	70	32	ELISA
Rasura	2013	Italy	NA	NA	NA	NA	101	101	*C. pneumoniae*	26	8	ELISA
Eini	2014	Iran	68.9	66.9	60/81	60/81	141	141	*C. pneumoniae*	111	74	ELISA
Cook	2016	UK	67.9	56.5	73/103	674/844	176	1518	*C. pneumoniae*	81	280	MIF
Bastiani	2008	Italy	76.6	76.5	51/55	51/55	106	106	*H. pylori*	67	57	UBT
Elkind	2000	USA	68.5	68.5	47/42	47/42	89	89	*C. pneumoniae*	72	74	ELISA
Elkind	2006	USA	72.3	72.3	125/121	219/38	246	474	*C. pneumoniae*	156	257	ELISA
Ebrahimi-Rad	2014	Iran	NA	NA	NA	NA	27	25	*C. pneumoniae*	20	13	ELISA
Hasan	2011	Iraq	58.02	56.1	18/32	18/22	50	40	*C. pneumoniae*	36	21	ELISA
Wincup	1996	UK	54	53.5	NA	NA	137	136	*H. pylori*	93	78	ELISA
Park	2006	Korea	66.7	66.8	62/63	62/63	125	125	*H. pylori*	100	75	ELISA
Heuschmann	2016	Germany	74.6	74.6	77/68	138/122	145	260	*H. pylori*	67	117	ELISA
Salmasi	2017	Iran	66.7	65.9	38/32	39/31	70	70	*H. pylori*	61	51	ELISA
Madre	2002	Spain	70	70	46/45	53/59	91	112	*C. pneumoniae*	40	34	IFI
Ķēniņa	2011	Latvia	65.8	64.3	41/61	22/26	102	48	*C. pneumoniae*	64	17	ELISA
Moayyedi	2003	UK	70.5	70.2	228/239	227/161	467	388	*H. pylori*	274	206	ELISA
Ngeh	2003	UK	NA	NA	59/41	60/27	100	87	*C. pneumoniae*	71	57	ELISA
Roham	2016	Iran	69.1	67.2	61/36	51/46	97	97	*M. pneumoniae*	4	0	ELISA
Ngeh	2004	UK	80	80	59/41	57/25	100	82	*M. pneumoniae*	95	82	ELISA
Njamnshi	2006	Cameroon	NA	NA	64/0	64/0	64	64	*C. pneumoniae*	41	35	ELISA
Rai	2011	India	53.6	38.6	16/35	14/34	51	48	*C. pneumoniae*	32	38	ELISA
Pietroiusti	2002	Italy	63.2	63.9	11/50	89/62	61	151	*H. pylori*	43	106	PCR
Wu	2014	Taiwan	53	53.2	1922/3882	1925/3879	5804	5804	*M. tuberculosis*	176	207	Culture

First Author	Year	Area	Age (year)		Gender (F/M)		Case group (n)	Control group (n)	Microorganism type	Number of bacterial infections (n)		Method
			case	control	case	control				case	control	
Bandaru	2009	India	35.3	35.3	30/90	30/90	120	120	*C.pneumoniae*	35	15	ELISA
Sheu	2014	Taiwan	33.5	42.4	824/1459	2939/3910	2283	6849	*M. tuberculosis*	136	256	Culture
Bandaru	2012	India	74	71	30/70	32/68	100	100	*C.pneumoniae*	29	16	ELISA
Tanne	2003	Israel	61	61	8/126	8/126	134	134	*C. pneumoniae*	115	110	ELISA
Gagliardi	2009	Brazil	NA	NA	25/40	37/22	65	59	*C. pneumoniae*	0	1	PCR
Voorend	2004	Netherlands	43.9	39.4	22/19	31/24	41	55	*C. pneumoniae*	28	38	ELISA
Grau	2001	Germany	62	59.5	36/73	27/55	109	82	*H. pylori*	57	34	ELISA
Wohlschlaeger	2005	Germany	65.1	73.3	5/5	16/7	7	21	*C. pneumoniae*	4	1	PCR
Anzini	2004	Italy	34.6	36.5	60/81	90/102	141	192	*C. pneumoniae*	2.9 (95% CI: 1.77–4.76)		ELISA
Johnsen	2005	Denmark	60.4	60.5	99/155	99/155	254	254	*C. pneumoniae*	1.28 (95% CI: 0.83–1.95)		ELISA
Sawayama	2005	Japan	71.5	69	22/40	95/48	62	143	*H. pylori*	9.68 (95% CI: 3.56–33.08)		UBT
Tarnacka	2002	Poland	74	66	91/88	66/56	179	122	*C. pneumoniae*	6.00 (95% CI: 1.61–22.29)		ELISA

2.4. Quantitative synthesis

Analyzing of data was done by use of Comprehensive Meta-Analysis (CMA) software version 2.2 (Biostat, Englewood, NJ). For this purpose, first the frequency of either bacterial infection including *H. pylori*, *C. pneumoniae*, *M. pneumoniae*, and *M. tuberculosis* for both case and control groups was measured and reported according event rate (%). Next, potential role of bacterial infection in forming and developing to ischemic stroke was calculated using Odds ratio (OR) with 95% Confidence intervals (CIs). Moreover, by Cochran's *Q* and I^2 statistic parameters, we analyzed heterogeneity of included studies. Based on our default, the cases with Cochrane *Q* statistic $p < 0.1$ and $I^2 > 25\%$ were considered as high heterogeneity cases. According to the Dersimonian and Laird method, the random effect model and the fixed effect model were applied in high heterogeneity and low heterogeneity cases respectively. Finally, Egger's regression was used for estimating asymmetry of funnel plot and also publication bias.

3. Results

3.1. Characterization of included studies

Regarding primary searching, 238 documents of 1996–2017 was identified and finally in accordance with inclusion criteria 50 studies were selected. Of these studies, 28, 18, 2, and 2 studies were related to *C. pneumoniae*, *H. pylori*, *M. pneumoniae*, and *M. tuberculosis* respectively. In addition, the diagnostic methods were included ELISA, PCR, UBT, MIF, IFI, and conventional microbiology. In the present study the information of 33,978 individuals including 13,652 patients (case) and 20,326 healthy (control) was investigated. Average of age in case and control groups was 61.7 and 59.8 respectively. The frequency of men in both case and control groups was measured 62.6% and 56.1% respectively. According to statistical analysis, the bacterial infection in both case (ischemic stroke) and control groups was 38% (37–39 with 95% CIs) and 26% (25–27 with 95% CIs) respectively. We also found a meaningful relationship between bacterial infections and progression into the ischemic stroke (OR: 1.704; 1.57–1.84 with 95% CIs; *p* value = 0.01; $I^2 = 78.55$; Q-value: 219.11; df = 47; Egger's intercept = 1.23).

3.2. The possible association between C. pneumonia infection and ischemic stroke

We found twenty articles which were about the role of infection by *C. pneumonia* in progression to stroke. The rate of infection was estimated in both stroke and healthy groups 57% (54–59 with 95% CIs) and 36% (34–37 with 95% CIs) respectively. A significant relevance was observed between infection by *C. pneumonia* and stroke (OR: 2.14; 1.91–2.38 with 95% CIs; p-value = 0.001; $I^2 = 71$; Q-value = 93.29; df = 27; Egger's intercept = 0.06).

3.3. The possible association between H. pylori infection and ischemic stroke

Of total of fifty case-control articles which was been included to this meta-analysis, eighteen articles were about the relevance of infection by *H. pylori* and stroke. The infection rate in both patient and healthy groups was 63% (60–65 with 95% CIs) and 55% (52–57 with 95% CIs) respectively. In accordance with statistical results, it seems that there is a meaningful relationship between infection by *H. pylori* and ischemic stroke (OR: 1.64; 1.44–1.87 with 95% CIs; *p* value = 0.001; I2 = 72.88; Q-value = 59; df = 16; Egger's intercept = 1.87).

3.4. The possible association between M. pneumonia infection and ischemic stroke

In relating of plausible role of infection by *M. pneumonia* and occurrence of ischemic stroke we found only two eligible studies. The incidence rate of infection in both case and control groups was 55% (39–70 with 95% CIs) and 47% (11–86 with 95% CIs) respectively. We did not find any significant relationship between *M. pneumonia* infection with ischemic stroke (OR: 0.97; 0.12–7.69 with 95% CIs; p-value = 0.98; I2 = 77.94; Q-value = 4.53; df = 1).

3.5. The possible association between M. tuberculosis infection and ischemic stroke

Finally, for evaluating the relevance between infection by *M. tuberculosis* and stroke we used two studies. Based on statistical analysis, the rate of infection by *M. tuberculosis* in both ischemic and age-gender matched healthy groups was 4% (3.6–4.5 with 95% CIs) and 3% (3.3-4 with 95% CIs) respectively. However, we observed a significant relationship between infection by *M. tuberculosis* and development into the ischemic stroke (OR: 1.15; 0.99–1.34 with 95% CIs; p-value = 0.05; I2 = 94.73; Q-value = 18.98; df = 1). Generally in the present study we appraised the potential role of bacterial infections by *C. pneumoniae*, *H. pylori*, *M. pneumoniae*, *M. tuberculosis*, and progression to ischemic stroke. In this meta-analysis we demonstrated a meaningful relationship between infection by three bacteria *C. pneumoniae*, *H. pylori*, and *M. tuberculosis* with occurrence of ischemic stroke. Nevertheless, the high heterogeneity and low validity of studies affected on our results. In addition, due to the limitation of results we could not evaluate the role of underlying factors such as age and gender.

4. Discussion

It is clear that the stroke is one of the most highlight cardiovascular disorders, and traditional risk factors including hypertension, diabetes mellitus, smoking, hyperlipidemia, atrial fibrillation, atherosclerosis, age, male sex, and positive family history can increase the risk of it (13). Predisposing risk factors for emerging and developing of stroke are different regarding differences in individuals, so that increase of stroke in the youth and its trend to autumn and winter shows some interfering modifiable risk factors that are not well known (14). In recent decades understanding of the role of acute and chronic infections in the occurrence of stroke is interested, so that various nested case-control studies have been conducted in this regard. Obviously infection can be lead to inflammation, which in turn triggers some complications such as formation of fatty plaques in the vessel wall, atherogenic reactions, and alteration in host metabolism (15). These changes are as underlying factors for affecting on CVDs especially ischemic stroke (Fig. 2). Of all, the infections caused by pathogens such as *C. pneumonia, H. pylori*, *M. pneumonia*, HIV, HSV 1–2, and CMV are more considerable, so that these infectious microorganisms have been frequently isolated from atherosclerosis plaque (16). On the other hand, induction of CIMT and high portion of seropositive population affected by CVD confirm this phenomenon (17). Nowadays there are several documents about the role of bacterial infections in increasing of stroke; for example, infective endocarditis causes to create emboli and arteritis. Moreover, bacterial meningitis and chronic brucellosis can be caused vasculitis and thrombosis in brain arteries, and likewise, rickettsial infections lead to damage of small vascular endothelial cells and the onset of ischemic stroke (14). In recent study the impressive role of bacterial infections in increasing of ischemic stroke was demonstrated, and using statistical analysis of fifty case-control studies we showed that there is a significant relationship between bacterial infection and ischemic stroke cases (OR: 1.7; CI: 1.5–1.8). *C. pneumonia* is a gram negative and obligate intracellular bacterium that was first introduced in 1980s. More than half of population is infected by this bacterium worldwide, and serological investigations has confirmed this fact (18, 19). In many studies researchers has isolated *C. pneumonia* from carotid plaques, atherosclerotic plaques, and circulating leukocytes (15). Sander et al. (2004) showed that eradication of *C. pneumonia* infection can be lead to stop CIMT (20). The clinical trial studies also have shown that the treatment of this infection can be caused reduction of vascular lesions in patients (21). In our study the rate of infection by *C. pneumonia* in both case and control groups was evaluated 57% and 36% respectively. Also, we showed that there is a meaningful relationship between infection by this bacterium and emergence of ischemic stroke (OR: 2.14; CI: 1.9–2.3). *H. pylori* is a spiral, gram negative, and microaerophilic bacterium which is colonized in human gastric sub-mucosa about half of the world's population (22). The rate of infection by this bacterium in developing countries is more than developed countries, so that in some regions of Africa infection by this pathogen reaches about 100% (23, 24). The bacterium is accounted as etiologic agent in disorders such chronic gastritis, peptic ulcer, as well as gastric cancer. However, *H. pylori*-related extra-gastrointestinal diseases have attracted a lot of attention, in which the relevance of *H. pylori* infection and CVD is well-known (25, 26). In addition to the several evidence regarding with isolation of *H. pylori* from atherosclerotic plaques, there are various documents about the effect of infection by this bacterium on some complications including insulin resistance, dyslipidemia, hypertension, and alteration in metabolism which describe the potential role of infection with this bacterium in increasing of ischemic stroke (27, 28). Based on our statistical analysis, the infection by this pathogen in both groups of ischemic stroke patients and age-gender matched healthy individuals was estimated 63% and 55% respectively. We observed a significant relationship between infection by this bacterium and development of ischemic stroke (OR: 1.6; CI: 1.4–1.8). *M. pneumonia* is one of the respiratory pathogens that in spite of poor understanding about its pathogenicity, many of people have anti-*M. pneumonia* antibodies (IgG and IgM). In recent several studies have noted to its role in extra-pulmonary manifestations such musculoskeletal, gastrointestinal, dermatologic, hematologic, neurological involvements, and cardiovascular complications (27, 29). According to review of the literature, near the 0.1% of infected to *M. pneumonia* will get neurological disability during their lives (30). The vasculopathies lesions caused as a result of this bacterial infection are indicating the role of *M. pneumonia* in increasing the ischemic stroke (14, 31). Two studies in this meta-analysis were related to the role of *M. pneumonia* in susceptibility to ischemic stroke; infection by this bacterium in both groups of case and control was 55% and 47% respectively. Also, based on statistical analysis we observed no significant relationship between infection by *M. pneumonia* and ischemic stroke (OR: 0.97; CI: 0.12–7.6). However, the low sample number could effect on outcomes, since only two studies allocated to this bacterium. In addition, high heterogeneity causes instability of results and we need furthermore studies in this regard. *M. tuberculosis* is one of the threatening pathogens of human life. Although this bacterium usually is known with the term "pulmonary tuberculosis", but it is a facultative intracellular pathogen which also has extra-pulmonary manifestations (32). In recent years the role of bacterium in promoting of neurological manifestation has been evaluated, so that in result of arterial invasion, malignant vasculitis can be occurred during the tubercular meningitis (14).

5. Conclusion

In the present study the information of two nested case-control studies about the role of *M. tuberculosis* in ischemic stroke was appraised. The rate of infection by this pathogen in both groups of case and control was 4% and 3% respectively; we found a significant relevance between mycobacterial infection

and ischemic stroke (OR: 1.1; CI: 0.99–1.34). In this study we assessed the relationship between bacterial infections and development of ischemic stroke. Nevertheless, due to limitation of in results we could not evaluate the role existing factors such age and sex in our research. Overall, for understanding the role of bacterial infections in ischemic stroke, it is better to do more studies about the association between bacterial infections and traditional ischemic stroke risk factors, carotid intima-media thickness, atherosclerosis, and cardiovascular risk factor such as LDL and HDL. Another limitation of our studies were including low sample number, excessive heterogeneity, potential publication bias, and low sturdy number in particular *M. pneumonia* and *M. tuberculosis*. We recommend further studies with more sample volume for determining the bacterial infection and their determinative role in ischemic stroke.

6. Abbreviations

Carotid intima-media thickness
CIMT
Cardiovascular disease
CVD
Cytomegalovirus
CMV
Hepatitis C virus
HCV
Human immunodeficiency virus
HIV
Herpes simplex virus type 1–2
HSV 1–2
Epstein Barr virus
EBV

7. Declarations

- Ethics approval and consent to participate

Not applicable (this paper was provided based on researching in global databases)

- Consent to publish

All authors have informed consent about the content of this paper.

- Availability of data and materials

All data will be available for anyone who requests those.

- Competing interests

There is no any conflict of interest among the all authors.

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- Authors' Contributions

1. MK was a major contributor in writing the manuscript
2. MK was research director and translated this manuscript to English

All authors read and approved the final manuscript

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8. References

1. Campbell BC, De Silva DA, Macleod MR, Coutts SB, Schwamm LH, Davis SM, et al. Ischaemic stroke. Nature Reviews Disease Primers. 2019;5(1):1–22.
2. Johnson CO, Nguyen M, Roth GA, Nichols E, Alam T, Abate D, et al. Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18(5):439–58.
3. Budzyński J, Wiśniewska J, Ciecierski M, Kędzia A. Association between bacterial infection and peripheral vascular disease: a review. Int J Angiol. 2016;25(01):003–13.

4. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. J Am Coll Cardiol. 2017;70(1):1–25.
5. Lucchese G, Flöel A, Stahl B. Cross-reactivity as a mechanism linking infections to stroke. Front Neurol. 2019;10:469.
6. Budzyński J, Koziński M, Kłopocka M, Kubica JM, Kubica J. Clinical significance of Helicobacter pylori infection in patients with acute coronary syndromes: an overview of current evidence. Clin Res Cardiol. 2014;103(11):855–86.
7. Kukreja N, Koslowski M, Insall R. Angiolymphoid hyperplasia with eosinophilia presenting as an axillary artery aneurysm. Case Reports. 2011;2011.
8. Sessa R, Di Pietro M, Filardo S, Turriziani O. Infectious burden and atherosclerosis: A clinical issue. World Journal of Clinical Cases: WJCC. 2014;2(7):240.
9. Chen BF, Xu X, Deng Y, Ma SC, Tang LQ, Zhang SB, et al. Relationship between Helicobacter pylori infection and serum interleukin-18 in patients with carotid atherosclerosis. Helicobacter. 2013;18(2):124–8.
10. Chen J, Zhu M, Ma G, Zhao Z, Sun Z. Chlamydia pneumoniae infection and cerebrovascular disease: a systematic review and meta-analysis. BMC Neurol. 2013;13(1):183.
11. Chen Y-W, Umeda M, Nagasawa T, Takeuchi Y, Huang Y, Inoue Y, et al. Periodontitis may increase the risk of peripheral arterial disease. Eur J Vasc Endovasc Surg. 2008;35(2):153–8.
12. Kelton JG, Neame PB, Gauldie J, Hirsh J. Elevated platelet-associated IgG in the thrombocytopenia of septicemia. N Engl J Med. 1979;300(14):760–4.
13. Muhlestein JB, Horne BD, Carlquist JF, Madsen TE, Bair TL, Pearson RR, et al. Cytomegalovirus seropositivity and C-reactive protein have independent and combined predictive value for mortality in patients with angiographically demonstrated coronary artery disease. Circulation. 2000;102(16):1917–23.
14. Grau AJ, Urbanek C, Palm F. Common infections and the risk of stroke. Nature Reviews Neurology. 2010;6(12):681–94.
15. Lindsberg PJ, Grau AJ. Inflammation and infections as risk factors for ischemic stroke. Stroke. 2003;34(10):2518–32.
16. Becker AE, de Boer OJ, van der Wal AC. The role of inflammation and infection in coronary artery disease. Annual review of medicine. 2001;52(1):289–97.
17. Szeto C-C, Chow K-M, Woo K-S, Chook P, Kwan BC-H, Leung C-B, et al. Carotid intima media thickness predicts cardiovascular diseases in Chinese predialysis patients with chronic kidney disease. J Am Soc Nephrol. 2007;18(6):1966–72.
18. Horn M. Chlamydiae as symbionts in eukaryotes. Annu Rev Microbiol. 2008;62:113–31.
19. Joshi R, Khandelwal B, Joshi D, Gupta OP. Chlamydophila pneumoniae infection and cardiovascular disease. North American journal of medical sciences. 2013;5(3):169.
20. Sander D, Winbeck K, Klingelhöfer Jr, Etgen T, Conrad B. Progression of early carotid atherosclerosis is only temporarily reduced after antibiotic treatment of Chlamydia pneumoniae seropositivity. Circulation. 2004;109(8):1010–5.
21. Illoh KO, Illoh OC, Feseha HB, Hallenbeck JM. Antibiotics for vascular diseases: a meta-analysis of randomized controlled trials. Atherosclerosis. 2005;179(2):403–12.
22. Yousefi B, Mohammadlou M, Abdollahi M, Salek Farrokhi A, Karbalaei M, Keikha M, et al. Epigenetic changes in gastric cancer induction by Helicobacter pylori. Journal of cellular physiology. 2019;234(12):21770–84.
23. Keikha M, Eslami M, Yousefi B, Ghasemian A, Karbalaei M. Potential antigen candidates for subunit vaccine development against Helicobacter pylori infection. Journal of cellular physiology. 2019;234(12):21460–70.
24. Bravo LE, van Doorn L-J, Realpe JL, Correa P. Virulence-associated genotypes of Helicobacter pylori: do they explain the African enigma? Am J Gastroenterol. 2002;97(11):2839–42.
25. Holcombe C. Helicobacter pylori: the African enigma. Gut. 1992;33(4):429.
26. Youssefi M, Ghazvini K, Farsiani H, Tafaghoudi M, Keikha M. A systematic review and meta-analysis of outcomes of infection with Helicobacter pylori dupA + strains in Iranian patients. Gene Reports. 2020:100650.
27. Guleria R, Nisar N, Chawla TC, Biswas NR. Mycoplasma pneumoniae and central nervous system complications: a review. J Lab Clin Med. 2005;146(2):55–63.
28. Kusters JG, Van Vliet AH, Kuipers EJ. Pathogenesis of Helicobacter pylori infection. Clin Microbiol Rev. 2006;19(3):449–90.
29. Khademi F, Vaez H, Momtazi-Borojeni AA, Majnooni A, Banach M, Sahebkar A. Bacterial infections are associated with cardiovascular disease in Iran: a meta-analysis. Archives of Medical Science: AMS. 2019;15(4):902.
30. Tsiodras S, Kelesidis I, Kelesidis T, Stamboulis E, Giamarellou H. Central nervous system manifestations of Mycoplasma pneumoniae infections. J Infect. 2005;51(5):343–54.
31. Ionita CC, Siddiqui AH, Levy EI, Hopkins LN, Snyder KV, Gibbons KJ. Acute ischemic stroke and infections. Journal of Stroke Cerebrovascular Diseases. 2011;20(1):1–9.
32. Keikha M, Soleimanpour S, Eslami M, Yousefi B, Karbalaei M. The mystery of tuberculosis pathogenesis from the perspective of T regulatory cells. Meta Gene. 2020;23:100632.

Figures

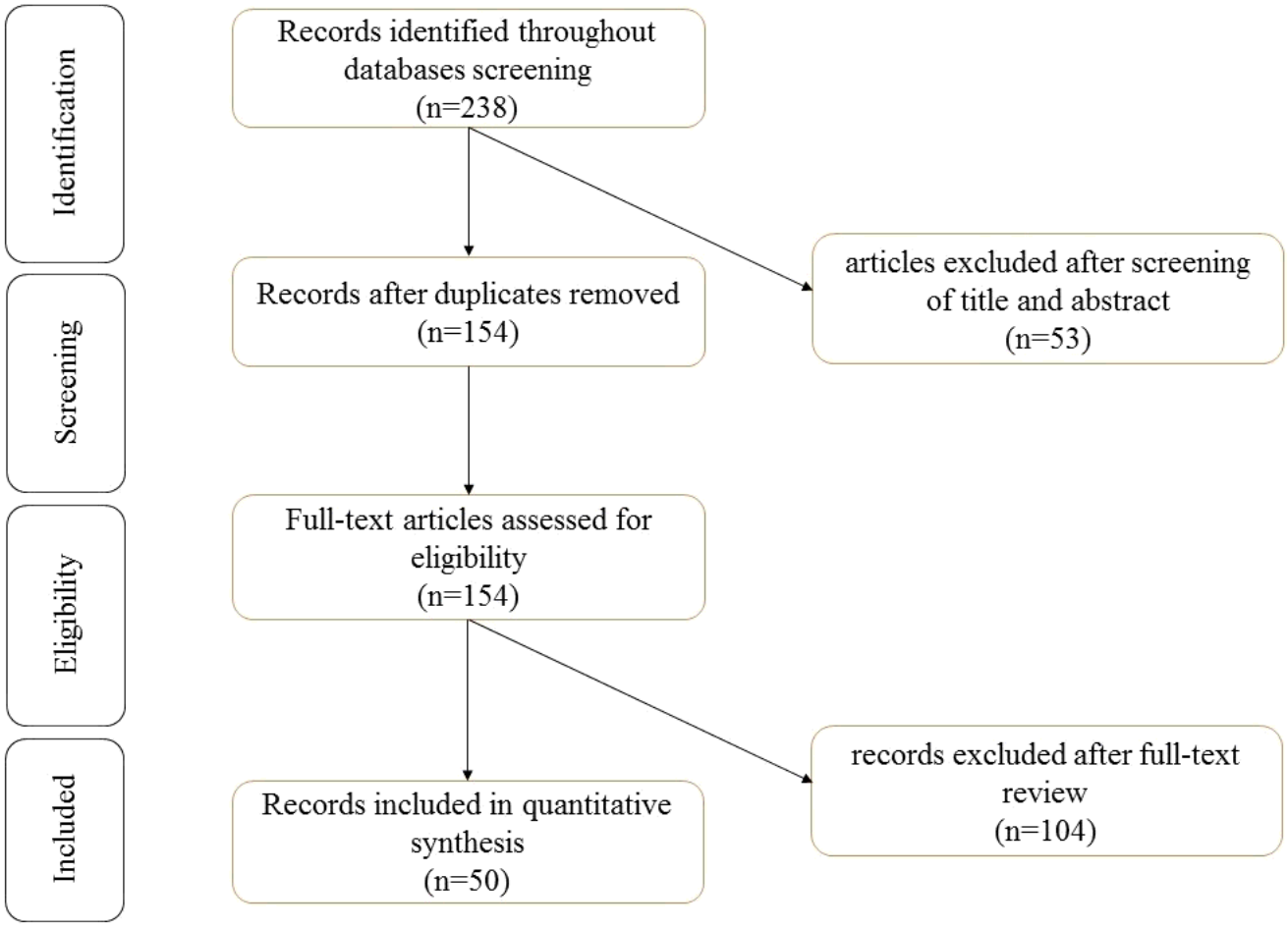

Figure 1

The flowchart of included studies.

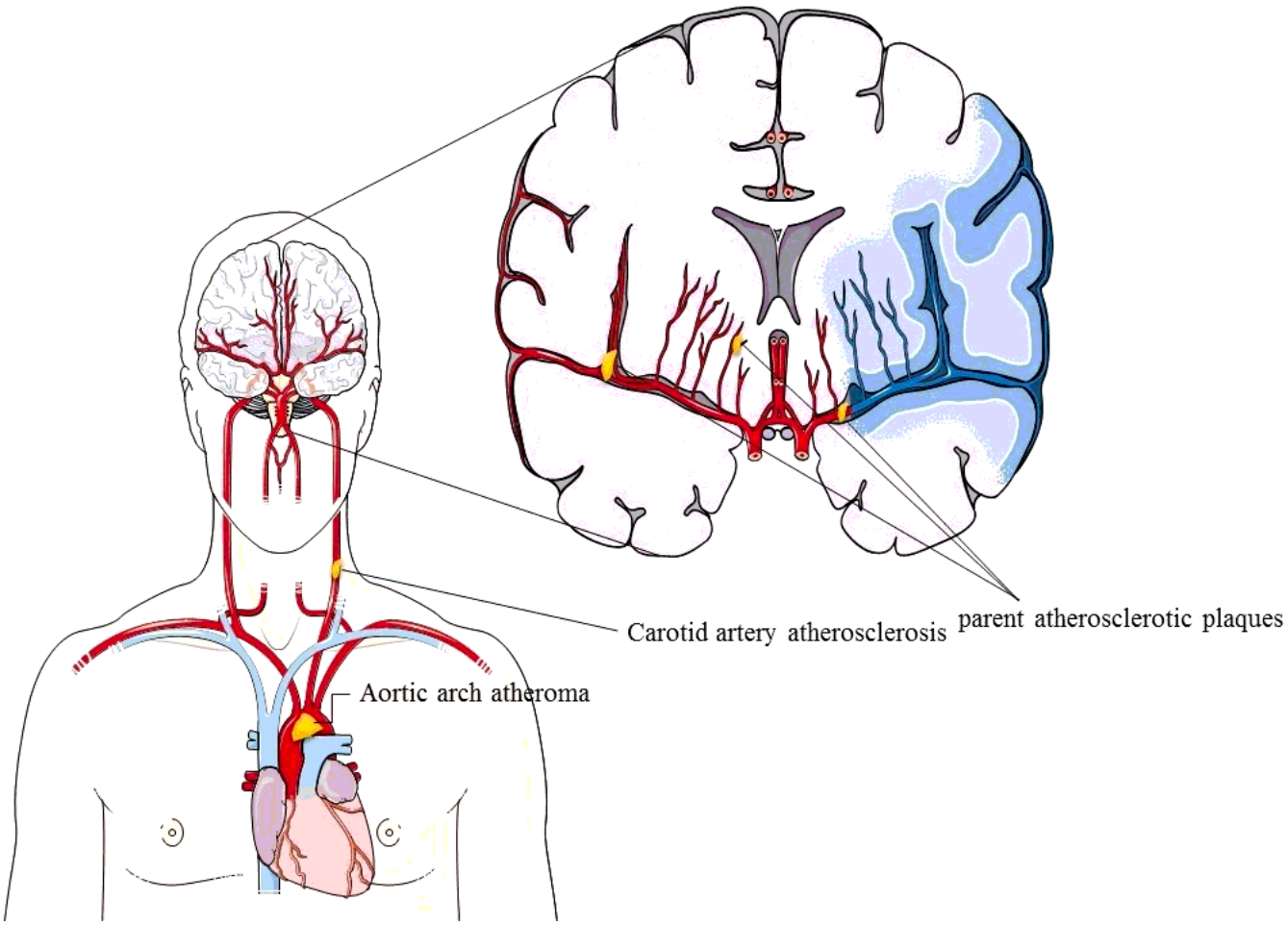

Figure 2

Cardiovascular disorders caused by infection. Bacterial infections cause some cardiovascular disorders including parent atherosclerosis plaques, Carotid artery atherosclerosis, and Aortic arch atheroma. This figure was taken from the website https://smart.servier.com/image-set-download/.

Supplementary Files

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- PRISMAchecklist.doc