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Association between *Mycoplasma pneumoniae* infection, high-density lipoprotein metabolism and cardiovascular health (Review)

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Abstract. The association between *Mycoplasma pneumoniae* (*M. pneumoniae*) infection, high-density lipoprotein metabolism and cardiovascular disease is an emerging research area. The present review summarizes the basic characteristics of *M. pneumoniae* infection and its association with high-density lipoprotein and cardiovascular health. *M. pneumoniae* primarily invades the respiratory tract and damages the cardiovascular system through various mechanisms including adhesion, invasion, secretion of metabolites, production of autoantibodies and stimulation of cytokine production. Additionally, the present review highlights the potential role of high-density lipoprotein for the development of prevention and intervention of *M. pneumoniae* infection and cardiovascular disease, and provides suggestions for future research directions and clinical practice. It is urgent to explore the specific mechanisms underlying the association between *M. pneumoniae* infection, high-density lipoprotein metabolism, and cardiovascular disease and analyze the roles of the immune system and inflammatory response.

Contents

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Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; CTL, cytotoxic T cell; Th, T helper; ApoA1, apolipoprotein A1; LCAT, lecithin-cholesterol acyltransferase; ABCA1, ATP-binding cassette transporter A1; SR-B, scavenger receptor class B; ROS, reactive oxygen species; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker

Key words: *Mycoplasma pneumoniae*, HDL lipoprotein metabolism, cardiovascular disease, association

1. Introduction

Mycoplasma pneumoniae (*M. pneumoniae*) is a small microorganism (2-5 μm) that is Gram-negative, lacking a cell wall, and can autonomously replicate (1). As a common pathogen, *M. pneumoniae* can cause pneumonia, especially in children aged between 5 and 15 years and older adults aged great than 50 years old. For children aged 5-15, *M. pneumoniae* infection accounts for 10-20% of hospitalizations for community-acquired pneumonia and to 30-40% during cyclic epidemics every 3-5 years (2,3). *M. pneumoniae* primarily causes acute respiratory infection and the clinical features involve multiple systems and include cough, asthma, shortness of breath, chest tightness and pain and fever (4). Due to the lack of cell wall, *M. pneumoniae* is resistant to β-lactam and macrolide antibiotics (5). However, *M. pneumoniae* is unable to survive independently and needs to parasitize host cells to grow and reproduce (6). The infection routes of *M. pneumoniae* include droplet transmission when the patient coughs, sneezes and speaks and close contact transmission, such as sharing utensils. *M. pneumoniae* is prone to cause outbreaks of pneumonia in group settings such as schools, the military and hospitals. In addition, these infections show seasonal epidemics, usually peaking in winter and early spring (7). *M. pneumoniae* infection can change the blood lipid content of patients and accelerate occurrence and development of cardiovascular diseases such as coronary heart disease and atherosclerosis (8-10).

High-density lipoprotein (HDL), an important lipoprotein in the body, plays a key protective and regulatory role via reverse cholesterol transport. HDL participate in the transport of cholesterol from extrahepatic tissues to the liver for metabolism (11). The primary function of HDL is to

transport excess cholesterol from tissues and cells to the liver for metabolism and excretion (12). HDL can prevent cardiovascular disease by removing excess cholesterol in the arterial blood vessel walls and reducing the risk of atherosclerosis. Lee-Rueckert *et al* (12) confirmed that the content of HDL is negatively correlated with onset of coronary heart disease. Antioxidants such as vitamin E and glutathione are abundant in HDL, which can maintain the integrity of vascular endothelial cells, neutralize peroxides to protect low-density lipoprotein (LDL) from oxidation and reduce the occurrence of atherosclerosis and arterial inflammation (13,14). HDL can reduce the inflammatory response by regulating adhesion and activation of inflammatory cells to maintain integrity and elasticity of the blood vessel wall and prevent cardiovascular disease such as atherosclerosis (15). Moreover, HDL can maintain normal flow of blood by inhibiting platelet aggregation and activation of coagulation factors (16), HDL also can regulate the formation and dissolution of thrombi in the blood by promoting the release of fibrinogen activators (17). In conclusion, antioxidant, anti-inflammatory and anticoagulant agents prevent atherosclerosis and decrease the risk of cardiovascular disease. Therefore, maintaining appropriate levels of HDL is key in maintaining cardiovascular health. However, whether *M. pneumoniae* infection can affect the blood HDL levels and the underlying mechanism require further investigation.

2. Pathogenesis of M. pneumoniae

M. pneumoniae, a pathogenic bacterium causing respiratory tract infections, lacks a cell wall. It is spherical or filamentous with a diameter of 2-5 μm and circular double-stranded DNA (1). The pathological changes resulting from the infection by *M. pneumoniae* are primarily interstitial pneumonia that affects the interstitial tissue of the lung with characteristics of inflammation, fibrosis or other abnormal changes, which can affect the oxygen exchange function of the lung (18). The pathogenesis of *M. pneumoniae* is complicated. The initial stage of *M. pneumoniae* infection is to adhesion to host bronchial cells, which can induce the changes in metabolism and structure of infected cells (Fig. 1). Adhesion between *M. pneumoniae* and epithelial cells is enhanced by various factors such as elongation factor thermo unstable. Invasion of *M. pneumoniae* directly damages host cells via deprivation of nutrition, release of toxins and production of H_2O_2. Moreover, infection by *M. pneumoniae* induces the generation of enzymes, lipids, lipoproteins and glycolipids, leading to the release of cytokines and inflammation that causes indirect damage. Furthermore, *M. pneumoniae* can invade the host immune system by degrading neutrophil extracellular traps, reactive oxygen species (ROS)/H_2O_2 and complement, causing long-term survival of *M. pneumoniae* and more severe damage to the body (19).

During the aforementioned process, unique lipoproteins on cell membrane of *M. pneumoniae* and the immune response of the body are key (19). Specifically, lipoproteins in *M. pneumoniae* such as P1, P30 and other adhesion-associated protein combine with the respiratory epithelial cell during *M. pneumoniae* infection. Therefore, *M. pneumoniae* can resist the clearance by mucosal cilia and phagocytosis and cause severe damage to host cells (20). The immune response involves humoral and cellular immunity (21). Humoral immunity refers to the activation of B lymphocytes binding to antigens such as bacteria, viruses, fungi and other pathogens, as well as other foreign molecules, and the production and action of specific antibodies (22). Stelmach *et al* (23) studied the dynamic changes and characteristics of serum-specific antibodies during *M. pneumoniae* infection and suggested that most patients develop *M. pneumoniae*-specific IgG, IgM, IgA and IgE. Cellular immunity primarily involves activities of immune cells including cytotoxic T lymphocytes (CTLs) and T helper (Th) cells to recognize and eliminate pathogens and abnormal cells. CTLs target and kill infected cells, while Th cells regulate the intensity and direction of immune responses (24,25).

Cytokines participating in both humoral and cellular immunity act as bridges within the immune system to ensure the coordination of these responses to defend the body against pathogens (26,27). In humoral immunity, cytokines such as IL-4, IL-5 and IL-6 secreted by Th cells can promote the differentiation of B lymphocytes into antibody-producing cells (plasma cells) and contribute to antibody production and antigen neutralization (28-30). In cellular immunity, cytokines such as IFN-γ secreted by activated T lymphocytes enhance the cytotoxic activity of cells such as CTLs and natural killer cells (NK) involved in cellular immune responses (24). In brief, cytokines are key mediators in both the clearance of pathogens and inflammation, however, the effect on the host tissue is complicated and cannot be predicted accurately due to the diversity of cellular and tissue environments (31,32). Moreover, the immune complexes comprising the antigen and corresponding antibody following *M. pneumoniae* infection can effectively activate the complement system, leading to removal of invasive microorganisms and immune damage of host multiple systems (33-35). He *et al* (36) demonstrated common antigen components between *M. pneumoniae* and host cells resulting in the evasion of host immune surveillance, hence contributing to long-term survival of *M. pneumoniae*.

M. pneumoniae can not only cause characteristic mycoplasmal pneumonia, but also leads to multiple extrapulmonary diseases involving cardiovascular system, skin, digestive tract and hematopoietic system (37,38). Narita (39) suggested that mechanisms of extrapulmonary manifestations caused by *M. pneumoniae* infection can be divided into three types: Direct damage caused by *M. pneumoniae* in the inflammatory site and local inflammatory cytokines induced by lipoprotein on the cell membrane; indirect immune damage such as autoimmunity or the formation of immune complexes caused by cross reactions between bacterial cell components and human cell components and local production of cytokines and chemokines, triggering vasculitis or thrombosis, which can obstruct the blood flow. *M. pneumoniae* colonizes specific organs through blood flow and the lipoproteins of the cell membrane can promote production of cytokines, ultimately leading to direct damage. The occurrence of autoimmunity is due to common antigens between *M. pneumoniae* and host cell components and expression of foreign antigens on host cell membranes due to infection. Additionally, formation and deposition of immune complexes are regarded as the

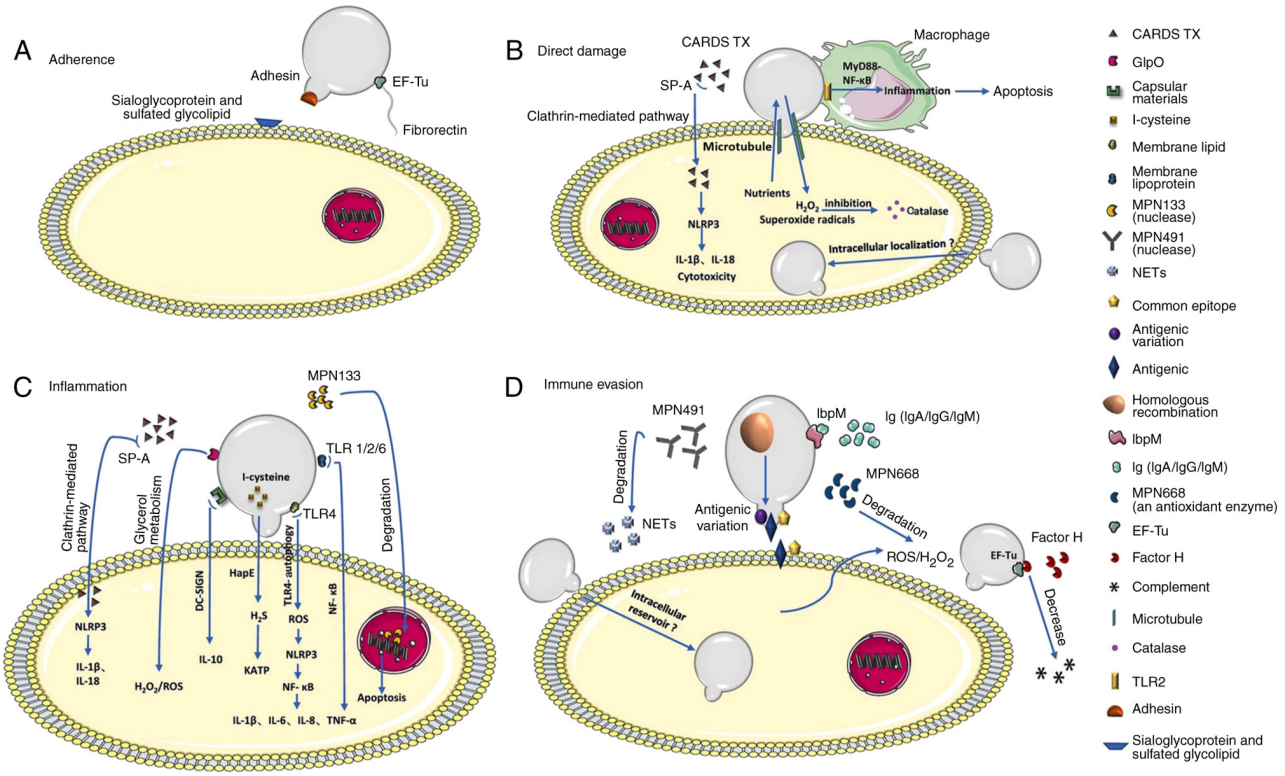

Figure 1. Pathogenesis of *M. pneumoniae* intrapulmonary infection. Adapted from (19). (A) *M. pneumoniae* adhesion causes cell damage. (B) *M. pneumoniae* releases toxin, H_2O_2 and superoxide radicals to cause indirect damage. (C) Pro-inflammation factors activate inflammatory response. (D) *M. pneumoniae* produces the nuclease to promote its immune evasion. EF-Tu, elongation factor thermo unstable; CARDS TX, community-acquired respiratory distress syndrome toxin; SP-A, surfactant protein A; GlpO, glycerol 3-phosphate oxidase; MPN, a secreted nuclease of *Mycoplasma pneumoniae*; NET, neutrophil extracellular trap; IbpM, immunoglobulin binding protein of *Mycoplasma*; ROS, reactive oxygen species; KATP, ATP-sensitive potassium channels; TLR, toll-like receptor; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; HapE, a alanine and hydrogen sulfide-producing enzyme.

pathological basis of *M. pneumoniae* extrapulmonary infection. *M. pneumoniae* in the bloodstream can induce TNF-α and IL-8, which cause vasoconstriction, leading to vascular occlusion (Fig. 2). However, the aforementioned mechanisms are not independent. In multifunctional organ failure related to *M. pneumoniae*, multiple mechanisms exist simultaneously (19).

3. Metabolism and function of HDL

The metabolism of HDL includes anabolism and catabolism. Fig. 3 depicts principal metabolic pathways as well as function of HDL (40). In synthesis, the backbone of HDL is apolipoprotein A1 (Apo A1), which is initially synthesized in the liver and small intestine and lipidated by ATP-binding cassette transporter A1 (ABCA1) to form pre-β HDL. Pre-β HDL can transform into mature HDL via the lipidation and mature HDL can become pre-β HDL under the role of endothelial (EL) and hepatic (HL) lipase. Catabolism occurs 4-5 days after maturity. HDL is catabolized in the liver via cell surface ATP synthase and cholesterol is removed by scavenger receptor class B type 1(SR-B1) in the kidney and liver (40).

The primary role of HDL is to transport cholesterol from peripheral tissue such as the cardiovascular system to steroidogenic tissues comprising testes, ovaries, and adrenal gland to product hormone. Moreover, it can exchange lipids with Apo B-containing particles such as LDL and very LDL (VLDL) via cholesterol ester transfer protein. Furthermore, HDL participates in reverse cholesterol transport, producing a marked antiatherogenic effect. Specifically, it can transport cholesterol from foam cells to the liver, metabolize it into bile and excrete it out of the body (40).

The protective role of HDL has been demonstrated in numerous types of diseases, such as metabolic (41) and cardiovascular disease (42) and cancer (43). Mitochondria are dynamic organelles that supply energy to the body and dysfunction is related to numerous kinds of disease, such as maternally inherited diabetes and deafness, the syndrome of metabolic defects, and autosomal dominant optic atrophy (44). Zheng *et al* (45) suggested that the occurrence and development of numerous types of diseases can be prevented and reversed via the role of HDL in preserving mitochondrial structure and function. Hence, understanding the mechanism concerning the effect of HDL on mitochondria will be beneficial for clarifying the pathogenesis of diseases including metabolic defects and providing new ideas for treatment. Moreover, HDL serves an important protective role in acute pancreatitis by inhibiting acinar cell pyroptosis (46). As a type of cell death, pyroptosis may contribute to initiation, progression, exacerbation and complications of atherosclerosis associated with activation of signal transducer, such as STAT3 (47). Thus, targeting pyroptosis may be a treatment method for atherosclerosis. Nevertheless, the relationships between HDL and mitochondria and pyroptosis are unclear.

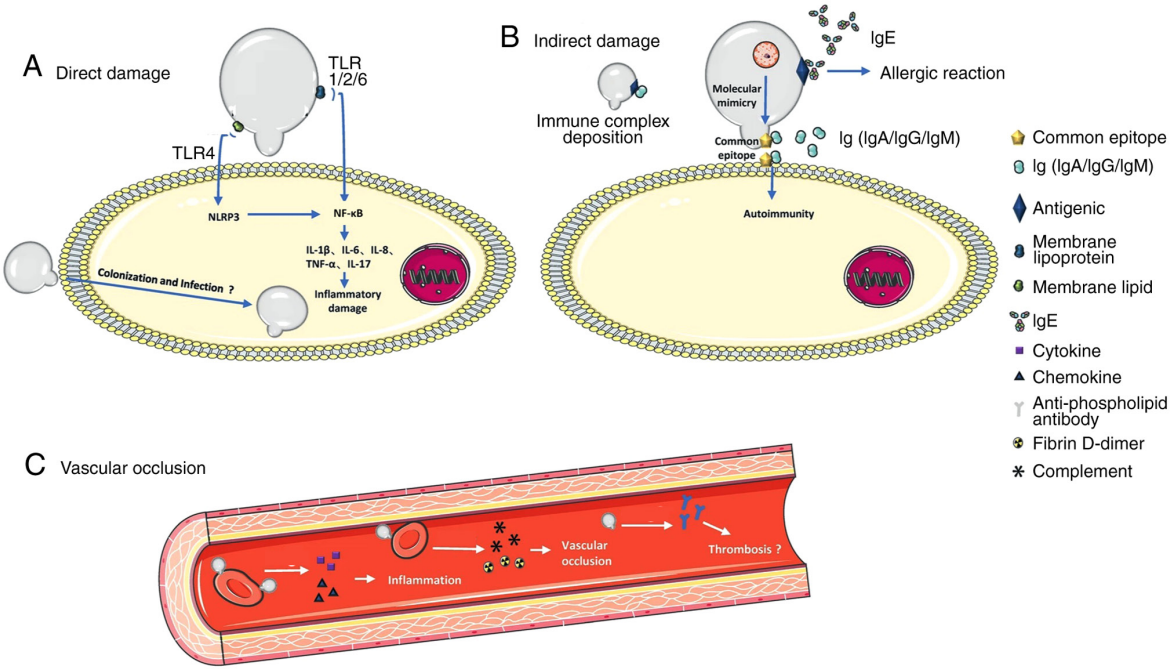

Figure 2. Pathogenesis of *M. pneumoniae* extrapulmonary infection. Adapted from (19). (A) *M. pneumoniae* invade leading to direct damage. (B) *M. pneumoniae* antigens cause immune complex deposition, autoimmunity, and allergic reaction. (C) *M. pneumoniae* induces vascular occlusion. TLR, toll-like receptor.

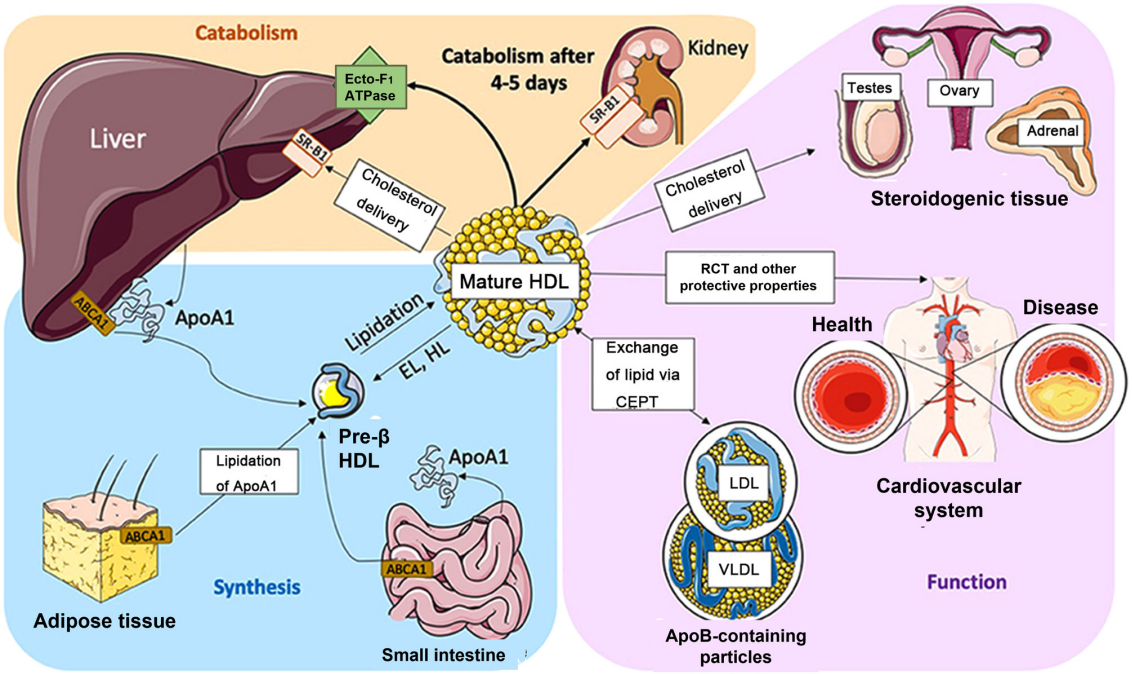

Figure 3. Metabolic pathway and function of HDL. Adapted from (40). ApoA1 and pre-β HDL are the precursor of mature HDL. The liver and kidney are the metabolic site of HDL. The function of HDL is to transport cholesterol from peripheral tissues to the liver for disposal, to steroidogenic tissues for generation of hormone; HDL, high-density lipoprotein; ecto-F_1-ATPase, ectopic cell surface F_1-ATP synthase; SR-B1, scavenger receptor class B type 1; Apo, apolipoprotein; ABCA1, ATP-binding cassette transporter A1; EL, endothelial lipase; HL, hepatic lipase; RCT, reverse cholesterol transport; CETP, cholesteryl ester transfer protein; VLDL, very low density lipoprotein.

4. Association between M. pneumoniae infection and HDL metabolism

According to Webb (48), HDL metabolism, including synthesis and degradation, is affected by human serum amyloid A protein in the acute phase of infection. Additionally, curcumin may lead to downregulation of genes related to HDL synthesis such as ApoA1 and then inhibit the synthesis of HDL particle (49,50). The inflammatory response caused by infection can release inflammatory cytokines that inhibit HDL synthesis

in hepatocytes (51,52). Infection promotes the degradation of HDL particles in the liver and other tissue, thereby decreasing their presence in the circulation (53). Moreover, oxidative stress and inflammatory responses caused by *M. pneumoniae* infection lead to degradation of HDL particles (54,55). However, the effects of *M. pneumoniae* infection on HDL synthesis and degradation pathways vary depending on factors such as study conditions, infection severity and individual differences. In addition, as studies are conducted *in vitro* or in animal models, there is an urgent need to elucidate the metabolic processes and influencing factors of HDL *in vivo* (32,38,40,51). In conclusion, *M. pneumoniae* infection can affect metabolism of HDL, however, further studies are needed to elucidate the specific mechanisms and clinical significance. Several studies have shown that *M. pneumoniae* infection can affect HDL-related gene expression and lipid metabolism (56-58). Specifically, *M. pneumoniae* infection changes expression levels of genes related to HDL synthesis and metabolism. For example, expression of ApoA1 protein is downregulated during the infection, which affects formation and function of HDL particles (59). Infection can affect the expression of other HDL-related genes such as *ApoA1* (60), lecithin-cholesterol acyltransferase *(LCAT) and ABCA1* (61), which affects the anabolism and catabolism of HDL. Inflammatory response and oxidative stress induced by *M. pneumoniae* infection can release cytokines including TNF-α, IL-1 and IL-6, which can affect the regulatory mechanisms of lipid metabolism and lead to lipid metabolism disorder such as elevation of plasma triglyceride and cholesterol levels (20). Moreover, inflammatory responses caused by infection can affect the stability and function of HDL; as a result, the ability of HDL to remove and transport cholesterol is impaired (62,63). Moreover, the immune response associated with infection also triggers a series of physiological changes such as alterations in hormone levels (estrogen and progesterone that regulate the synthesis and metabolism of HDL in the body (64-66).

M. pneumoniae is a common respiratory pathogen that can cause pneumonia, bronchitis and other upper respiratory tract infections (67). HDL, a key lipoprotein in the blood, can remove excess cholesterol from arterial walls and transport it back to the liver to be metabolized and eliminated, thus protecting the cardiovascular system (68,69). *M. pneumoniae* infection is associated with decreased HDL levels by enhancing the inflammatory response and disrupting lipid metabolism, which promote cholesterol deposition in the arterial wall and increase risk of atherosclerosis and cardiovascular disease (9). However, the association between *M. pneumoniae* infection and HDL levels is not clear due to differences in study sample size, study design and clinical characteristics of the disease; other influencing factors between infection and HDL levels need to be further explored. In addition, potential confounding factors such as age and sex, lifestyle, substance use, genetic factors and nutritional status need to be considered.

The biological mechanisms by which *M. pneumoniae* infection affects HDL metabolism are complex and involve multiple physiological and pathological interactions. *M. pneumoniae* infection triggers an inflammatory response in the host that produces cytokines such as IL-1 and TNF-α, which directly or indirectly affect HDL metabolism (70,71). In addition, the inflammatory response can inhibit HDL synthesis and promote HDL metabolism, thereby decreasing levels of HDL (72). During *M. pneumoniae* infection, cell surface receptors associated with HDL binding and uptake such as SR-BI, SR-BII and CD36 by cells also change, resulting in decreased metabolism and clearance of HDL (73,74). More specifically, SR-BI is a high-affinity HDL receptor expressed widely in tissues such as the liver, kidneys, adrenal cortex and intestines; as a crucial cell membrane protein, it promotes the selective uptake of HDL and reverse cholesterol transport (75,76). Similar to SR-BI, SR-BII is also an HDL receptor, but its expression levels are lower, hence, SR-BII is less efficient than SR-BI in reducing the level of plasma HDL (77,78). In addition, CD36 serves an important role in regulating lipid metabolism and cellular uptake by binding to HDL and interacting with other lipid-loaded molecules such as LDL and fatty acids (79,80). These receptors are key in regulating cholesterol metabolism, lipid transport and other physiological processes associated with lipid balance and different cells and tissue may express different types of HDL receptors to adapt to their specific metabolic needs. Studies have shown that specific immune cells such as macrophages and lymphocytes are associated with HDL metabolism and serve a crucial role in fighting *M. pneumoniae* infection (19,81,82). The infection triggers oxidative stress and generates a large number of free radicals that alter HDL lipid fractions and function and ultimately decrease the antioxidant capacity and metabolic stability of HDL (83). In addition, other factors such as delivery of inflammatory mediators and the interaction between lipids and protein can also regulate HDL metabolism (84). Currently, although there are many studies on effects of the infection on HDL metabolism, the specific mechanisms still need to be further elucidated (79,81,83). Understanding these mechanisms may help to understand the effects of *M. pneumoniae* infection on HDL levels and provide novel strategies for the prevention and treatment of *M. pneumoniae* infection.

In addition, infection can regulate HDL-related metabolic enzyme activities (85). Studies have shown that infection leads to downregulation of expression of HDL synthases including LCAT and HDL transporter proteins such as ABCA1 in the liver and other tissue, which affects the production of HDL and inhibits maturation of HDL following the infection with severe Acute Respiratory Syndrome Coronavirus 2 (86), Coronavirus disease 2019 (COVID-19) (87) and *Helicobacter pylori* (88). More specifically, LCAT plays a crucial role in converting free cholesterol into cholesteryl esters, which is an essential process for HDL function (89). Inflammatory cytokines produced during infections can influence LCAT activity, and lead to changes in the composition and function of HDL (90,91). ABCA1 is another key protein involved in HDL metabolism via facilitating efflux of cellular cholesterol, which is a key step in HDL synthesis (92,93). Jacobo-Albavera *et al* (94) suggested that expression of ABCA1 can influence a broad array of diseases covering inflammation, infection, coronary heart disease, thrombosis, and cancer progression.

Oxidative stress occurs when there is an imbalance between production of ROS and the ability of body to neutralize them; factors including infection can contribute to oxidative stress (95,96). During infection, immune cells produce ROS to combat pathogens; excessive or prolonged inflammation can further increase oxidative stress (97). ROS, highly reactive

molecules, can damage various cellular components including DNA, lipid and proteins (98). Oxidative stress triggered by *M. pneumoniae* infection oxidizes lipid components of HDL such as phospholipids and cholesterol, which results in structural changes in the lipoprotein and decreases its ability to function effectively (99,100). As a result, the ability of HDL to remove excess cholesterol from cells and prevent formation of fatty deposits in blood vessels is impaired. Moreover, oxidized HDL loses anti-inflammatory and antioxidant functions, hence, it is unable to remove oxidized LDL and oxidized products existing in cells (101,102). Additionally, oxidized HDL can be pro-inflammatory and pro-atherogenic, which promotes development of atherosclerosis through hardening and narrowing of the arteries (103). Maintaining balance between antioxidants and ROS is key for preserving integrity and functionality of HDL. While there is evidence suggesting that infections influence HDL-related metabolic enzyme activities, more research is needed to establish a direct link between *M. pneumoniae* infection and HDL metabolism (102,103).

5. Association between cardiovascular health, *M. pneumoniae* infection and HDL metabolism

The cellular composition of heart, a vital organ, includes cardiomyocytes, fibroblasts, myofibroblasts and inflammatory cells such as macrophages (104,105). Myofibroblasts synthesize extracellular matrix to replace dead cardiomyocytes, however, the regeneration rate of cardiomyocytes is low (106,107). The heart can work effectively in with a small number of dead cells, but if the death is wide and severe, the heart cannot repair itself, resulting in arrhythmia and heart failure (108,109). The cardiovascular system, also known as the circulatory system, comprises the heart, arteries, capillaries and veins, and serves key functions in the maintenance of normal life activities. Specifically, it can supply organs and tissues with oxygen and nutrients and transport waste to excretory organs (110).

Several studies have validated the association between HDL and cardiovascular risk and considered the cholesterol in HDL as a key element to predict cardiovascular disease (72,111,112). However, it is uncertain whether causality between HDL and cardiovascular risk exists. At present, clinical trials associated with increasing HDL concentration and promoting HDL function have not yet been completed (103,109,111,113). Further research is needed to explore treatment methods to changing the metabolism and function of HDL (113). Additionally, the molecular mechanism of HDL expression is complicated and may involve multiple proteins, bioactive lipids and non-coding RNA (113).

Certain antiphospholipid antibodies such as anticardiolipin antibody and lupus anticoagulant are found in the blood of patients with cardiovascular system disease and can be raised during *M. pneumoniae* infection through interaction between *M. pneumoniae* cell wall components and human phospholipids (39). However, the potential mechanism underlying how *M. pneumoniae* infection regulates occurrence and development of disease related to the cardiovascular system is incompletely understood. At present, direct links between *M. pneumoniae* infection and long-term cardiovascular health are not clear (8). While respiratory infections caused by *M. pneumoniae* trigger an acute inflammatory response, whether the association between the infection and cardiovascular complications result from inflammatory response is unclear (114). Consequently, identifying the mechanisms underlying cell death and cardiac damage during *M. pneumoniae* infection is of importance.

Studies have suggested that certain types of respiratory infection, including *M. pneumoniae* can increase short-term risk of cardiovascular events (38,39,115). For example, acute infection can trigger inflammatory response, which may destabilize pre-existing atherosclerotic plaques and increase risk of cardiovascular events such as heart attacks and stroke (115-117). In addition, the 'infectious burden hypothesis' suggests that chronic or repeated infection may contribute to development of atherosclerosis and cardiovascular disease via hardening and narrowing of arteries over time (118). Moreover, infection can trigger an ongoing inflammatory response that leads to persistent oxidative stress and damage to blood vessel walls, which is a promoting factor for formation of atherosclerotic plaque (119,120).

Restrepo and Reyes (8) suggested that the inflammatory response triggered by *M. pneumoniae* infection can interfere HDL metabolism, decreases the level of HDL and increase risk of cardiovascular events. According to Badimon and Vilahur (121), some cytokines resulting from inflammatory response promote platelet aggregation and improve coagulation activity and increase the risk of thrombosis; hence, the probability of adverse cardiovascular events such as heart attack and stroke significantly increases. A prolonged inflammatory state can also promote he progression of atherosclerosis via promoting cholesterol deposition and damaging artery walls (122). Furthermore, *M. pneumoniae* infection can cause myocarditis that impairs myocardial function and cardiovascular health in children (123,124). *M. pneumoniae* infection can lead to activation or suppression of immune system, and the effects of dysregulated immune function on the cardiovascular system such as coronary heart disease, myocardial infarction, heart failure, arrhythmia, and myocarditis are also confirmed (125). However, cardiovascular health is influenced by numerous factors including malnutrition, physical disability, dyslipidemia, dysglycemia, hypertension, adiposity, thrombosis, kidney dysfunction and demographic and genetic factors (126,127). Therefore, the impact of *M. pneumoniae* infection on cardiovascular health is likely to vary between individuals. To determine the exact mechanism and better understand potential links between *M. pneumoniae* infection and cardiovascular health, further research including long-term prospective studies and clinical trials is necessary.

6. Prevention and intervention strategies

Prevention of *M. pneumoniae* infection mainly includes washing hands frequently and maintaining good personal hygiene, avoiding crowded places especially during epidemics, avoiding close contact with patients infected with *M. pneumoniae*, opening windows regularly to maintain good indoor air circulation, maintaining adequate sleep and balanced diet and consulting the doctor promptly (20,128,129). *M. pneumoniae* infection is a self-limited disease, meaning it can recover without treatment (130). However, infection

can lead to serious complications in high-risk groups such as the elderly (131) and those with a compromised immune system (20) or chronic illnesses (132). Therefore, it is key to develop more measures to prevent the infection with *M. pneumoniae*.

There are preventive or treatment strategies proposed to improve prognosis of patients with pneumonia caused by *M. pneumoniae* and decrease the incidence of cardiovascular disease. Statins, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are commonly used and effective drugs (8,129,131). Feldman and Anderson (133) demonstrated that the long-term use of statins contributes to lower incidence of pneumonia and associated cardiac injury. Moreover, statins inhibit the activity of β-hydroxy-β-methylglutaryl-CoA reductase to reduce cholesterol levels and stimulate the liver to uptake LDL from the blood, which has a notable impact on preventing cardiovascular diseases especially coronary heart disease (134,135). Alexander *et al* (136) claimed that ACE inhibitors can reduce the risk of community-acquired pneumonia hospitalization and mortality. ACE is involved in generation and regulation of angiotensin, while ACE inhibitors decrease the generation of angiotensin II, thus, lowering blood pressure, improving heart function, and alleviating cardiovascular burden (137,138). ARB can block angiotensin II receptors, leading to vasodilation and decreased blood pressure (139). ARBs are commonly prescribed as a treatment for hypertension (140,141), heart failure (142) and certain kidney conditions (143). However, the side effects of these drugs cannot be ignored; for example, statins increase the death risk of sepsis or ventilator-associated pneumonia (144). Drug selection and combination therapy are crucial for treatment of diseases de Gomensoro *et al* (145) suggested that immunizations can reduce the risk of major cardiovascular complications related to infection. With the mutation and outbreak of influenza, the American Heart Association and American College of Cardiology has recommended influenza vaccination for patients with cardiovascular disease such as coronary atherosclerosis (146). According to Mohseni *et al* (147), Behrouzi *et al* (148) and Saade *et al* (149), influenza vaccination can reduce cardiovascular complication and cardiovascular-related mortality. Besides the influenza vaccination, pneumococcal vaccination also serves a protective role among high cardiovascular risk populations (150). However, the mechanism and specificity of vaccines against *M. pneumoniae* is unclear; it is an urgent need to clarify whether targeted vaccination decreases the incidence of cardiovascular complications (151).

7. Conclusion

At present, there is limited evidence of an association between *M. pneumoniae* infection, HDL metabolism and cardiovascular disease. In the future, it is urgent to explore the specific mechanisms between *M. pneumoniae* infection and HDL metabolism and analyze the roles of the immune system and inflammatory response. In addition, large-scale epidemiological investigations and clinical studies are also needed to assess the potential association between *M. pneumoniae* infection and cardiovascular disease and the role of HDL metabolism therein. Moreover, the regulatory mechanism of the immune system during *M. pneumoniae* infection also needs further investigation to develop effective vaccines to prevent *M. pneumoniae* infection and decrease risk of infection-induced cardiovascular complications. In conclusion, in-depth study of the relationship between *M. pneumoniae* infection and HDL metabolism is key for the prevention and treatment of cardiovascular and other associated disease.

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Availability of data and materials

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Authors' contributions

TS and LK designed the study and wrote the manuscript. YaL, TL, and YuL reviewed and edited the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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