Do Childhood Infections Contribute to Adult Cardiometabolic Diseases?

David Burgner, PhD,*†‡ Richard Liu, MBBS,*† Melissa Wake, MD,*† and Cuno S. P. Uiterwaal, PhD§

Cardiometabolic disease (CVD) and related metabolic conditions—together termed “cardiometabolic diseases”—account for much of the increasing global morbidity and mortality rates from noncommunicable disease.1 They account for more than twice the number of deaths from cancer and the disease burden is predicted to increase over the coming decades. Traditional cardiovascular risk factors (hypertension, diabetes mellitus, obesity, hypercholesterolemia, and smoking) do not account for all the attributable risk.2 Recent paradigm shifts in the understanding of these adult-onset conditions are that cardiometabolic diseases may have their origins very early in life and that risk parameters track from childhood into adulthood.3,4 Pathological changes, which may be partly reversible, accumulate silently for decades before causing disease in adulthood. Therefore, childhood remains a largely overlooked opportunity for prevention. The American Heart Association has stated that “cardiovascular disease is largely preventable”5; however, effective primordial (ie, prevention of risk factors themselves) and primary prevention require an understanding of the very early determinants of risk.

Cardiometabolic diseases are multifactorial, chronic inflammatory conditions.6,7 Inflammatory responses begin in infancy, and these trajectories may persist into later life.8 On the one hand, these responses are protective; inflammation is a fundamental host response to infection, especially early in life during the maturation of the adaptive immune system. On the other, it seems that persistent inflammatory responses are ultimately maladaptive, with higher levels of inflammatory markers predicting clinical events and adverse outcomes9; phase III trials specifically targeting inflammatory pathways are currently under way in adults with CVD.6

There is thus considerable interest in the role of infection in the development of cardiometabolic risk and disease. This relationship was first suggested in the late 19th century, when rabbits infected with salmonella or streptococci after minor arterial injury developed more severe atherosclerosis.10 Here, we briefly review more recent human data on childhood infection and cardiometabolic diseases, including whether a single or multiple pathogens are implicated, the relationship of infection and inflammation with traditional risk factors, and the possible role of antibiotic exposures and the possible effects on the microbiome.

METHODOLOGICAL CONSIDERATIONS

Most human data on infection and cardiometabolic diseases come from case-control studies in adults, where historical evidence of exposure to a small number of candidate pathogens is deduced primarily from serology. This approach is pragmatic but generally not informative about the timing of infection, clinical severity or degree of inflammation, and is possibly liable to reverse causality (ie, those with established cardiometabolic disease may be more susceptible to infections). The interval between childhood infectious exposures and adult CVD is long, and by and large, the childhood studies that have now reached this endpoint in large numbers (ie, participants born before approximately 1955) did not consider such exposures. Consequently, many studies use intermediate phenotypes of cardiovascular risk (such as carotid intima-media thickness and measures of arterial elasticity), which in adults are predictive of later CVD.11 However, as these techniques have only been applied to younger children relatively recently, the long-term predictive value of these childhood phenotypes remain uncertain.12

ONE PATHOGEN OR MULTIPLE?

Both single pathogens and the total pathogen burden could contribute to cardiometabolic disease. Individual pathogens most consistently implicated include Chlamydia (formerly chlamydia),13 Helicobacter,14 Cyto- megalovirus (CMV) and other herpes viruses,16 and hepatitis C virus.16 There are supportive animal data (eg, from experimental models of atherosclerosis) for some pathogens (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/C241). Cardiovascular risk and events are also increased in HIV infection in adults, and adverse intermediate phenotypes and increased inflammation are found in vertically infected children, arising from HIV infection per se and from antiretroviral therapy.17

CANDIDATE PATHOGENS

Chlamydia and Helicobacter are the most studied candidate pathogens for CVD, with data largely from cross-sectional serological studies in adults. Microbial DNA from Chlamydia, Helicobacter and CMV has been identified in atherosclerotic plaques.18–20 It has been suggested that Chlamydia in particular may directly infect and damage the arterial wall. Childhood infection with Chlamydia has been associated with increased markers of atherosclerosis in imaging studies of the carotid artery and aorta, as well as abnormalities in arterial function.21,22 Although longitudinal studies of these single pathogens are sparse, adult data indicate that levels of Chlamydia endotoxin are increased some months before a cardiovascular event,23 and that persistently elevated CMV antibodies are associated with adverse intermediate phenotypes (increased carotid intima-media thickness, increased blood pressure and endothelial dysfunction)24 and CVD mortality.25

The ESPID Reports and Reviews of Pediatric Infectious Diseases series topics, authors and contents are chosen and approved independently by the Editorial Board of ESPID.
Pathogen-specific infection has also been suggested to modulate later metabolic risks. In adults, infection with these candidate pathogens has been associated with proatherogenic lipid profiles, although the limited pediatric data do not indicate that similar effects occur in childhood. There has also been particular interest in adenovirus-36 and the development of later obesity, with supportive data from animal, in vitro studies, and cross-sectional human studies. However, a recent analysis of paired samples from child and adult does not seem to support a causal role.

PERIODONTAL DISEASE

The contribution of bacteria involved in periodontitis (chronic infection of the tooth pocket and gums) to systemic inflammation and CVD has been the subject of considerable investigation, particularly in adults. There is evidence that endotoxin and DNA from periodontal pathogens are present in atherosclerotic lesions, and that interventions that aggressively treat periodontitis may reverse adverse inflammatory cardiovascular risk phenotypes.

PATHOGEN BURDEN

Given that inflammation is a generic innate host response, an attractive concept is that it is the total pathogen burden—rather than a single pathogen—that modulates cardiometabolic risk. Unfortunately, pathogen burden and the resulting inflammatory response are difficult to quantify, especially retrospectively. For pragmatic reasons, pathogen burden is often inferred from positive serology for a limited number of candidate pathogens. Although necessarily giving an incomplete picture, these data support an association with CVD events (myocardial infarction, ischemic stroke and peripheral vascular disease). In children, prospective data suggest that, in the months following even a relatively trivial viral infection, there is endothelial dysfunction (one of the earliest changes in atherosclerosis development), increased carotid intima-media thickness, and a proatherogenic lipid profile. It remains to be seen if these changes persist or whether the repeated (and usually trivial) infectious insults typical of childhood have a cumulative effect. Children exposed to cigarette smoke and infection have increased arterial stiffness and accelerated atherosclerosis, suggesting infection may modulate the effects of traditional cardiovascular risk factors.

LONGITUDINAL DATA

Population-level statistical data, available in some settings, allow the use of hospitalization with infection as a proxy marker of infection burden. Although most childhood infections do not result in hospitalization, infection is the commonest reason for childhood admission, and hospitalization is less prone to differences in health-seeking behavior than emergency department or primary care attendances. In Western Australia, where population-based data linkage commenced in 1970, there is a dose–response relationship between infection-related hospitalization in childhood (<18 years) and CVD events in adulthood (>18 years). The association is independent of traditional risk factors that can be identified from population-level data. However, this cohort is relatively young and may represent a more extreme CVD phenotype; as the population born after 1970 ages, it should become apparent whether the findings are more broadly applicable. A similar approach using statutory data from Finland has shown relationships between infection-related hospitalization, particularly in the preschool child, and adult obesity, metabolic syndrome and some adverse cardiovascular intermediate phenotypes. Although infection-related hospitalization per se did not show a significant social gradient, associations with adult cardiometabolic disease were only observed in children raised in families of lower socioeconomic status, suggesting infection may be a mediator on the causal pathway underlying social gradients in cardiometabolic diseases (Liu R, Burgner DP, unpublished data). Similar results linking infection-related hospitalization and adult obesity have been reported in Danish men.

These associations between infection-related hospitalization and cardiometabolic parameters have a number of plausible (and nonexclusive) explanations. The severe infections themselves (and/or the resulting severe acute inflammation) could directly damage blood vessels. Hospitalizations may be a marker for children susceptible to more infection and inflammation overall (most of which does not result in hospitalization) and therefore may also be an indicator of children who may receive more antibiotics earlier in childhood.

INFECTION OR ITS TREATMENT?

Childhood infections are often treated empirically with antibiotics. A retrospective study in adolescents indicated a positive association—indeed of traditional risk factors—between the number of courses of macrolides in childhood and adverse cardiovascular parameters in adolescence, suggesting that antibiotic use may be an informative measure of infection burden and/or that antibiotics may have direct effects themselves. Recent data have implicated antibiotic exposures both before birth and in childhood with later obesity. Antibiotics alter the microbiome, especially when given early in life, which in turn may affect cardiometabolic risk. Animal data have shown that transfer of the fecal microbiome from obese to lean mice leads to obesity without a change in diet. In atherosclerosis, human and animal data suggest that microbial metabolism of dietary choline results in a proatherosclerotic metabolite that is strongly associated with CVD events, independently of traditional risk factors. Investigation and manipulation of the microbiome in cardiometabolic disease is likely to be a rapidly expanding field.

CONCLUSIONS AND FUTURE DIRECTIONS

An old idea—that infection may increase cardiometabolic risk—has survived well over a century of investigation and intermittent skepticism. Recent epidemiological research increasingly and consistently supports the presence of an association, although there remains a high potential for residual confounding. Ecological population studies could provide powerful support by quantifying differential rates of infection and/or use of antibiotics across countries and relating these to differential inflammation and cardiometabolic outcomes. If upheld, causation of cardiometabolic risk could occur via childhood infection itself, the inflammation that it elicits, and/or antibiotic treatment. The effects are likely to be part of causal pathways that also include traditional risk factors. With rapidly improving “–omics” technology and bioinformatics, mechanistic data should help identify both those at greatest risk and possible interventions. Given the long preclinical period in the development of cardiometabolic diseases, modulation of infectious and inflammatory determinants in childhood may emerge as an important approach to reducing the “epidemic in slow motion” of adult cardiovascular and metabolic diseases.

REFERENCES

5. Weintraub WS, Daniels SR, Burke LE, et al; American Heart Association Advocacy Coordinating Committee; Council on Cardiovascular Disease in the Young; Council on the Kidney in Cardiovascular Disease;


