

# Challenges in ischaemic heart disease: not sleeping enough, not brushing your teeth, and skipping breakfast—three ways of increasing your risk of myocardial infarction?

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## KEYWORDS

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Despite optimal medical therapies, there is currently a persistent residual cardiovascular risk. The most likely pathway responsible for this residual risk has been identified in the *inflammatory state*. Recent studies have confirmed that inflammation increases cardiovascular risk independently from LDL cholesterol levels. Addressing traditional risk factors, such as obesity, cigarette smoking, diabetes, arterial hypertension, and dyslipidaemia, also provides an important reduction of the levels of inflammation. Nonetheless, inflammation is also a target for specific and focused therapeutic interventions. Recent studies have outlined an association between oral hygiene, sleep deprivation, and nutritional patterns on the one hand, with the development of multi-districts atherosclerosis and/or adverse cardiovascular events on the other. These lifestyle patterns appear to be involved in fostering inflammation associated with atherosclerosis. There is, however, a persistent need for further studies to clarify whether such associations with cardiovascular disease are direct and causal, and if they are all channelled through vascular inflammation.

## Introduction

Cardiovascular disease is still currently the main cause of morbidity and mortality worldwide. Atherosclerosis is a progressive ‘inflammatory’ disease, where besides age, disease progression is affected by well-known risk factors, such as diabetes, smoking, obesity, hypertension, and dyslipidaemia, the early treatment of which is universally recommended. The persistent occurrence of cardiovascular events despite medical therapy considered ‘optimal’ is called ‘residual risk’, an example being the occurrence of events despite the achievement of extremely low

cholesterol-LDL (C-LDL) targets (<30 mg/dL), as demonstrated by recent trials. Inflammation has been hypothesized to be the main common pathway of this residual risk.<sup>1</sup>

## Emerging ‘strange’ lifestyle associations with cardiovascular risk and their likely common mechanism

The fundamental role of chronic low-grade inflammation in mediating all stages of atherosclerotic disease, from endothelial dysfunction to atherothrombotic complications,<sup>2</sup> is well known. Studies have recently been published highlighting new and unexpected associations between specific behavioural habits and the development of multiple-district atherosclerosis, and/or cardiovascular

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events. There is initial evidence that such new, previously unexpected associations, may have inflammation as a common disease pathway.

## Sleep deprivation

Sleep deprivation is a common condition in developed countries, so much so that, according to current evidence, we sleep on average 1.5 h less every day than in the last century. Although to date a real causal relationship between sleep deprivation and cardiovascular risk has not been definitely confirmed, epidemiological studies and experimental data indicate a strong association with the development of cardio-metabolic risk factors, multiple-district atherosclerosis and coronary artery disease.<sup>3</sup> Various pathophysiological mechanisms have been proposed to explain the possible link between sleep deprivation and cardiovascular disease. Both sleep deprivation and poor-quality sleep are associated with significant changes in various biological systems. Specifically, sleep deprivation has been associated with autonomic dysregulation, endothelial dysfunction, hypercoagulability, insulin resistance, and systemic inflammation. Adrenergic hyperactivation is mainly responsible for the development of arterial hypertension through vasoconstriction, tachycardia, and salt retention. Furthermore, a dysregulation of the autonomic nervous system, through inhibition of pancreatic function and increased cortisol levels, has been associated with the development of insulin resistance, hyperglycaemia, and full-blown diabetes. In addition to this, sleep deprivation facilitates the development of obesity through an altered release of ghrelin and leptin, which are mainly responsible for the increased sense of hunger.<sup>4</sup>

Although several epidemiological studies had previously shown a possible association between sleep deprivation and cardiovascular disease, they were limited by small sample sizes and the lack of validated tools that objectively measured the quality and quantity of sleep. More recently, the results of a study that examined the association between sleep duration and sleep fragmentation on the one hand, and the development of multiple-district, coronary, and non-coronary subclinical atherosclerosis, have been published. The study included 3974 subjects from the Progression of Early Subclinical Atherosclerosis (PESA) registry. They were subjected for 7 days to a recording of qualitative and quantitative parameters of sleep. Based on the total hours of sleep recorded, four groups were identified: a group of subjects who slept <6 h, one who slept between 6 and 7 h, one who slept between 7 and 8 h, and the last group of subjects who slept more than 8 h. Through imaging techniques, such as 3D ultrasonography of the carotid and femoral districts and computed tomography of the coronary arteries, the prevalence and progression of subclinical vascular atherosclerotic lesions were identified. After statistical adjustment for conventional risk factors, the authors found that a shorter sleep period was independently associated with a higher multiple-district atherosclerotic 'load' compared to the reference group. Specifically, subjects who slept <6 h were 27% more likely to have multiple-district atherosclerosis than those who

slept 7-8 h. In addition, subjects with higher sleep fragmentation were 34% more likely to have multiple-district atherosclerosis than those who had good sleep quality.<sup>5</sup> In the light of this, both sleep duration and its quality would appear to be independently associated with the development of multiple-district subclinical atherosclerosis, and therefore would emerge as important therapeutic targets. In addition to systemic inflammation, in this case, the autonomic dysregulation and a propensity to cardiac arrhythmias/sudden death could also play a pathogenetic role.

## Poor oral hygiene

Poor oral hygiene is the main cause of periodontal disease, a complex chronic inflammatory disease of the tissues surrounding the teeth, and one of the most common chronic infections associated with a moderate and constant systemic inflammatory response.<sup>6</sup> In the last two decades, an increasing interest has been directed to the link between periodontal disease and cardiovascular diseases. Inflammation is known to play an important role in the pathogenesis of atherosclerosis, and in this sense inflammation markers, high in periodontal disease, have been consistently associated with a higher risk of cardiovascular disease.<sup>7</sup> In a prospective cohort study published in 1995, De Stefano *et al.* examined more than 9000 subjects belonging to the First National Health and Nutritional Examination Survey (NHANES I) Epidemiologic Follow-up Study. After 15 years of follow-up, and after statistical adjustment for multiple confounders, the investigators showed that subjects suffering from the periodontal disease had a 25% increase in the risk of coronary heart disease compared to those with mild periodontal disease.<sup>8</sup> In a study of another subsequent cohort using combined data from the Normative Aging Study and the Dental Longitudinal Study, Beck *et al.* showed that in subjects with more severe periodontal disease the risk of coronary heart disease and fatal coronary events was significantly higher than in those with the milder periodontal disease even after adjustment for the various cardiovascular risk factors (the odds ratio was 1.5 for coronary heart disease and 1.9 for fatal coronary events, respectively).<sup>9</sup> Although the pathophysiological rationale was consistent, the result of two subsequent meta-analyses was not conclusive. A first meta-analysis, conducted by Bahekar *et al.* and published in 2003, confirmed that having a periodontal disease increases the risk of cardiovascular disease, but this increase was not statistically significant.<sup>10</sup> On the contrary, a second meta-analysis, published soon after in 2004 by Meurman *et al.*,<sup>11</sup> concluded for an association of periodontal disease/poor oral health with cardiovascular disease. The first study that considered the frequency of daily teeth brushing and its possible association with systemic inflammation and the risk of cardiovascular disease as an oral hygiene measure was published in 2010. A sample of the Scottish Health Survey comprising 11 869 subjects with no known cardiovascular disease at baseline was examined. In addition, in a subset of 4830 patients, the investigators assessed the existence of an association between brushing the teeth a few times and finding increased blood levels of

C-reactive protein (CRP) and fibrinogen, markers of inflammation and, for the second, also of hypercoagulability. A total of 555 global cardiovascular events had occurred during an average 8-years follow-up, of which 70 had been fatal. Seventy-four % of total cardiovascular events were attributed to coronary heart disease. After adjusting for various confounders, subjects who brushed their teeth poorly had a higher risk of cardiovascular disease (hazard ratio 1.7; 95% confidence interval 1.3-2.3;  $P < 0.001$ ). They also had increased blood concentrations of CRP and fibrinogen.<sup>12</sup> In this sense, unlike the first epidemiological studies that used clinical evaluation to diagnose periodontal disease, a simpler parameter such as the number of times you brush your teeth appears to be useful and very cost-effective in carrying out large-scale population studies.

## Skipping breakfast

It is well known that dietary habits are potential targets for primary prevention strategies. Skipping breakfast is considered a frequent and unhealthy habit. Dietary patterns have changed significantly in recent decades. It has been estimated that 20-30% of adults today skip breakfast. There is no evidence that skipping breakfast is associated with the development of subclinical atherosclerosis with a consequent increase in cardiovascular morbidity and mortality. Small prospective studies have in fact highlighted how the habit of skipping breakfast is associated with the presence of various cardiometabolic risk factors, including weight gain, dyslipidaemia, arterial hypertension, and diabetes.<sup>13</sup> Altered metabolic patterns as a consequence of this habit appear to occur early, already in paediatric-adolescent age, as evidenced by Shafiee *et al.* in 2013 in a study conducted on 5625 subjects aged between 10 and 18 years. School students were here divided into three groups, based on the number of times they took breakfast during the week. The investigators showed that the risk of metabolic syndrome, defined according to the criteria of the Adult Treatment Panel III modified for children, was significantly higher in the group of students skipping breakfast compared to those who regularly took it. In fact, breakfast skippers featured significantly higher average values of triglycerides, LDL-C, blood pressure, and body mass index.<sup>14</sup> More recently, a study published by Uzhoka *et al.* has provided important additional evidence to this association, demonstrating the presence and distribution of subclinical vascular atherosclerotic lesions in people skipping breakfast. Specifically, this study assessed the association between taking breakfast or not, as well as its quality characteristics, with objective evidence of subclinical atherosclerosis. Using vascular ultrasonography and cardiac computed tomography, they analysed the carotid, ilio-femoral, and aortic vascular districts, as well as coronary calcium with the calcium score. A statistical cross-sectional sampling analysis was done within the PESA registry, including asymptomatic adults without known heart disease at baseline. Three breakfast models were defined: high-energy breakfast, defined as more than 20% of the daily energy intake; low-energy breakfast, defined as 5-20% of the total daily intake; and 'breakfast skipping', as in subjects who took <5% of their daily energy intake at

breakfast, combined with those totally skipping breakfast. After statistical corrections for traditional cardiovascular risk factors and other confounders, the authors reported that, compared with subjects taking breakfast regularly, skippers had more multiple-district atherosclerosis with a higher prevalence of non-coronary atherosclerosis.<sup>15</sup> In a completely adjusted model the habit of skipping breakfast was associated with coronary artery calcium (CAC) values greater than 100; this association was not statistically evident for CAC levels between 0 and 100. This should not be surprising considering that subclinical atherosclerosis is usually identified earlier in the iliac-femoral, carotid, and aortic districts compared to coronary arteries. Obviously, the study had important limitations: in particular, completely separating the effects of breakfast from other dietary and non-dietary risk predictors, and establishing how regular breakfast intake is an independent marker of atherosclerosis is very difficult from a statistical standpoint. Although an association between food patterns and cardiovascular risk needs further confirmation, the important message of the study remains: the habit of skipping breakfast is at least an important marker for identifying categories at increased cardiovascular risk on which to direct preventive and therapeutic measures more effectively.

## Conclusions

To date, it is known that treatment of traditional cardiovascular risk factors such as obesity, smoking, diabetes, high blood pressure, and dyslipidaemia is critically associated with a reduction of systemic and vascular inflammation. If inflammation, as it looks like, plays an important role in atherothrombotic disease, the pathophysiological substrate of increased systemic inflammatory response would explain the association between poor oral hygiene and the risk of cardiovascular events.<sup>7</sup> Sleep deprivation and the habit of skipping breakfast could be responsible for an increased systemic inflammatory response indirectly, through the development of cardiometabolic risk factors, with a possible role of autonomic dysregulation.<sup>3,13</sup>

We still, however, need larger studies to verify whether such observed associations with cardiovascular disease are really causal or more simply risk markers. But because of their high prevalence in the general population, it is easy to understand how their control might have a huge epidemiological impact. On the basis of these recent acquisitions, it is likely that advices on lifestyle changes, relatively easy to implement on a large scale and potentially very cost-effective, could contribute to reducing cardiovascular morbidity and mortality, adding-up to the already known and more publicized list of preventive measures.

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