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Review article

Two cosmoses, one universe: a narrative review exploring the gut microbiome's role in the effect of urban risk factors on vascular ageing

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ABSTRACT

In the face of rising global urbanisation, understanding how the associated environment and lifestyle impact public health is a cornerstone for prevention, research, and clinical practice. Cardiovascular disease is the leading cause of morbidity and mortality worldwide, with urban risk factors contributing greatly to its burden. The current narrative review adopts an exposome approach to explore the effect of urban-associated physical-chemical factors (such as air pollution) and lifestyle on cardiovascular health and ageing. In addition, we provide new insights into how these urban-related factors alter the gut microbiome, which has been associated with an increased risk of cardiovascular disease. We focus on vascular ageing, before disease onset, to promote preventative research and practice. We also discuss how urban ecosystems and social factors may interact with these pathways and provide suggestions for future research, precision prevention and management of vascular ageing. Most importantly, future research and decision-making would benefit from adopting an exposome approach and acknowledging the diverse and boundless universe of the microbiome.

1. Introduction

Across the globe, our environments are becoming increasingly urbanised and are simultaneously encroaching on previously rural settings [1]. With this ever-changing environment, understanding the impact of this urban transition on our health is a priority, particularly with projections demonstrating that nearly 70 % of the global population will live in cities by 2050 [1]. Urbanisation impacts the environmental risk factors that we are exposed to on several levels, altering surrounding ecosystems, lifestyle, and social factors, whilst being exposed to new physical-chemical elements [2], the sum of these environmental factors is known as the exposome [3,4]. These urban-related factors have been linked to an increased risk of cardiovascular diseases (CVD) [5], which are the leading cause of illness and death worldwide [6]. The rising rates of CVD, in part due to an ageing population and the epidemiological transition, are increasing the burden on healthcare and the economy. This trend necessitates increased efforts towards implementing scalable and preventive measures to postpone the onset of CVD, consequently slowing down the ageing process of the cardiovascular system [7]. The current review focuses on vascular ageing (VA) to facilitate efforts in the early detection and prevention of CVD. We define VA as pathological abnormalities resulting in atherosclerosis, arterial stiffness (AS), elevated blood pressure (BP)/hypertension (HT); and CVD, as well-established cardiac and vascular entities.

Gaining a deeper understanding of how these urban environmental risk factors impact VA could pave the way for enhanced prevention and treatment. In this context, internal exposome factors, such as the human gut microbiome (GM), have received little consideration despite GM's close association with the urban environment [8] and promising role in

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Abbreviations

AIx	augmentation index
AP	air pollution
AS	arterial stiffness
BP	blood pressure
cf	carotid-femoral
CRF	corticotropin-releasing factor
CVD	cardiovascular disease
CVH	cardiovascular health
DASH	Dietary Approaches to Stop Hypertension
GM	gut microbiome
HPA	hypothalamic-pituitary-adrenal
HT	hypertension
LPS	lipopolysaccharides
NCDs	non-communicable diseases
NO_2	nitrogen dioxide
PM	particulate matter
$PM_{2.5}$	Particulate matter with a diameter of 2.5 μm
PM_{10}	Particulate matter with a diameter of 10 μm
PWV	pulse wave velocity
SCFA	short-chain fatty acid
SO_2	sulfur dioxide
TMA	trimethylamine
TMAO	trimethylamine-N-oxide
VA	vascular ageing

cardiovascular health (CVH) [9]. Specifically, urban-induced changes in air pollution (AP), lifestyle, as well as low soil biodiversity might lead to microbial dysbiosis and subsequent disease [8]. These urban risk factors might contribute to the chronic loss of microbial diversity in both the environment and in humans [10]. However, the precise impact of these environmental-induced GM changes on VA remains unclear [11].

The current narrative review aims to discuss the role of GM in the association between urban-environmental risk factors and VA. We adopt an exposome approach that considers the cumulative and interactive components within urban ecosystems and factors associated with urban lifestyles, social connections, and physical-chemical properties. Due to the limited scope of this paper, we focus on the major risk factors, such as AP and urban lifestyles, given their significant burden on CVD and GM. In the discussion, we explore how other urban components, such as social connections and urban ecosystems, may interplay and exacerbate these relationships. This holistic approach considers the vast and interconnected universe of the microbiome, encompassing both the human body and the surrounding environment (Fig. 1). Furthermore, we draw attention to the areas where scientific knowledge is currently lacking and provide insights into future directions for clinical practice and research, with the goal of improving cardiovascular prevention and treatment.

2. Methods

We searched Embase, Ovid (Medline), Web of Science, and Google Scholar to identify articles reporting the associations between urban environmental risk factors and GM with VA until 22nd July 2023. The search strategy combined the terms related to alcohol, ambient air pollution, arterial stiffness, atherosclerosis, blood pressure, VA, cardiovascular disease, cardiovascular health, diet, dietary interventions, exposome, food groups, gastrointestinal microbiome, gut microbiota,

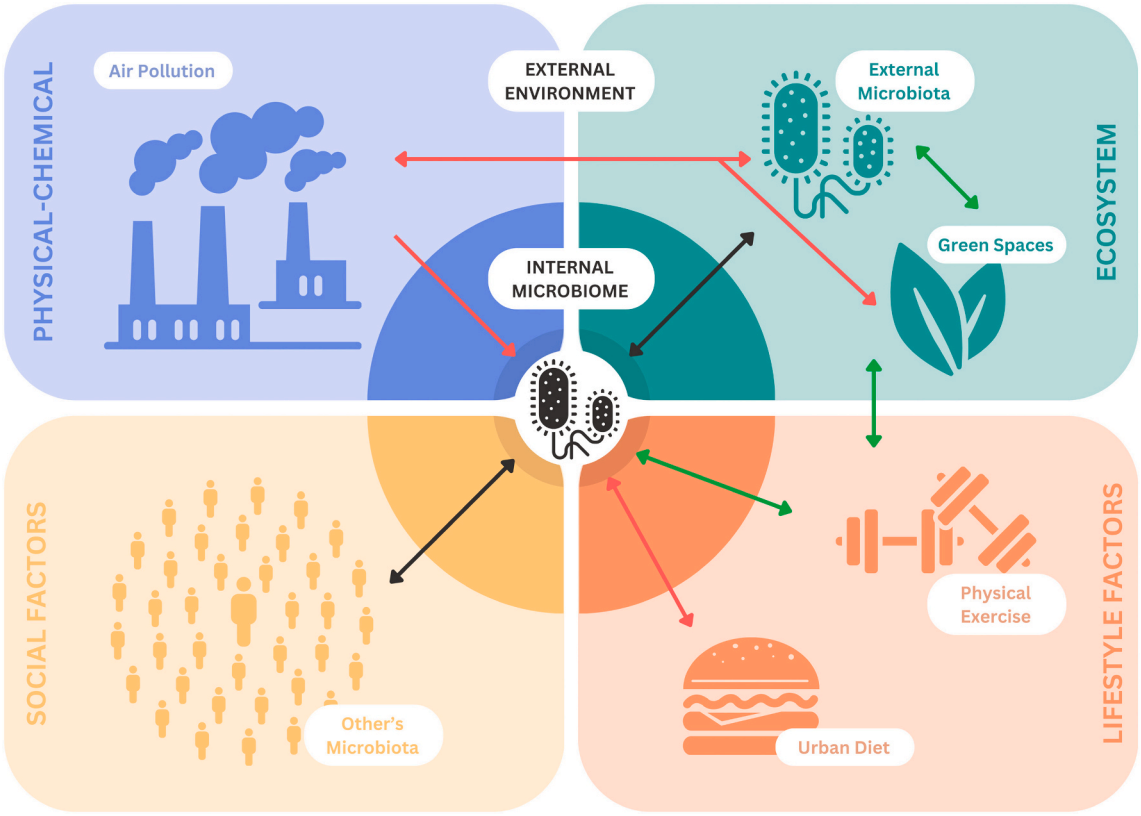

Fig. 1. A schematic illustration of the links between urban environmental factors and external and internal microbiota: The two cosmoses (external and internal microbiota) have high transmissibility; thus, should be considered as one interconnected universe where all are susceptible to urban environmental factors.

hypertension, lifestyles, macronutrients, micronutrients, nutrition, particulate matter, physical activity, smoking, tobacco, and urbanisation. We translated the search strategies from Embase to the other databases (Supplementary Table 1). Due to the nature of this narrative review, we prioritised the most recent (published in the last ten years) and relevant publications in the field. Regarding the type of studies, umbrella reviews, meta-analyses, and systematic reviews were prioritised, in that order over individual studies. When a summary of the evidence was not available, narrative reviews or original studies were considered. Among original studies, prospective cohorts were selected over other designs. We excluded letters to the editor, editorials, and conference reports.

3. How do urban pollutants impact vascular ageing?

3.1. Overview

Emerging evidence has pointed out the detrimental impact of environmental pollution on CVH [6]. Traditional pollutants (e.g., unsafe water sources and sanitation) and their collective burden on disease have long been a public health concern, mainly associated with poor living conditions [12]. However, modern pollutants, such as those associated with industrial and urban development, including AP, have far surpassed traditional pollutants, and are now considered one of the main risk factors for non-communicable diseases (NCDs), including CVD [12]. In addition, due to their ambient nature, modern pollutants affect entire populations for longer. Thus, their cumulative effect is a global threat, with pollution already underpinning 16 % of deaths globally and is expected to rise with climate change [12].

So far, research has uncovered a variety of chemical pollutants that could impact CVH, including AP, water pollution, occupational pollution, and toxic metals such as lead [13]. Non-chemical pollutants (e.g., transportation noise and light) have also been linked to CVD, albeit less than ambient AP [13]. Of these pollutants, particulate matter (PM) is the most dangerous form of AP [14] due to its higher penetration capacity and cumulative effect over time [14]. Particularly, PM with a diameter of 2.5 μm ($PM_{2.5}$) or less has been linked to CVD [14] through elevated BP, acute coronary syndrome, myocardial infarction, cardiac arrhythmia, and heart failure [15].

3.2. The association between air pollution and vascular ageing markers

While the research linking ambient AP to CVD has increased substantially, the available literature on specific VA markers is limited. Table 1 summarises the findings of an umbrella review [16] investigating the effect of short and long-term exposure to AP (PM and nitrogen dioxide (NO_2)) on multiple CVD outcomes, including VA markers (e.g., atherosclerosis, AS, and elevated BP/HT).

Regarding short-term exposure to PM, NO_2, and sulfur dioxide (SO_2), higher levels of $PM_{2.5}$ and PM with a diameter of 10 μm (PM_{10}) were associated with an increased augmentation index (AIx) and ankle-brachial pulse wave velocity (PWV). These pollutants produce endothelial dysfunction and reduce NO_2 activity, modifying vascular tone and vasoconstriction [16,17]. Furthermore, all pollutants were associated with higher diastolic BP (except SO_2) and the risk of HT, whereas only $PM_{2.5}$ produced changes in systolic BP [16]. Short-term exposure also produces alteration/stimulation of the autonomic and sympathetic nervous systems and increases BP while decreasing cardiac flow (Fig. 2). Finally, this review remarks on a lack of evidence on atherosclerosis.

The findings from long-term exposure are inconsistent for AS. There was no association of $PM_{2.5}$ with AS, whereas higher levels of NO_2 and SO_2 increased carotid-femoral (cf)-PWV and AIx [17]. On the other hand, $PM_{2.5}$ was associated with atherosclerosis [16,18], diastolic BP, and the risk of HT [16]. As for the mechanisms potentially explaining these effects, long-term AP might induce structural vascular changes by remodelling the extracellular matrix. In addition, it could participate in atherogenesis. At later stages, AP might contribute to increasing

Table 1
Summary of findings in systematic reviews and meta-analysis evaluating the association between AP and vascular ageing markers.

Exposure duration	Air pollutant	Vascular ageing markers
Short-term	PM including: $PM_{2.5}$, PM_{10}	Atherosclerosis: Not evidence available. Higher levels of PM Arterial stiffness: - Increased AIx and AP - Increased ab-PWV (statistically significant 4/5 studies).
	$PM_{2.5}$	For every 10 μg/m^3 increase in $PM_{2.5}$ Blood pressure and HT: - Higher DBP and SBP - Increased risk of HT
	PM_{10}	For every 10 μg/m^3 increase in PM10 Blood pressure and HT: - Higher DBP - Increased risk of HT
	NO_2	Atherosclerosis – Not evidence available. Arterial stiffness: Not associated with AIx and ab-PWV Blood pressure and HT: - Not associated with SBP - Higher DBP - Increased risk of HT
	SO_2	Atherosclerosis: Not evidence available. Arterial stiffness: Positive associated with AIx and AP Blood pressure and HT: - Not associated with SBP or DBP - Increased risk of HT
Long-term	$PM_{2.5}$	For every 10 μg/m^3 increase in $PM_{2.5}$ Atherosclerosis: - Increased CMIT per year - Positive associated with CMIT (statistically significant 6/9 studies). - Increased CAC per year - Positive associated with CAC (statistically significant 4/7 studies). Arterial stiffness: - Not associated with ABI - Not associated with cf-PWV or AIx Blood pressure and HT: - Higher DBP - Increased risk of HT
	PM_{10}	For every 10 μg/m^3 increase in PM10 Atherosclerosis: Not associated with CMIT Blood pressure and HT: - Higher DBP - Less consistent the risk of HT
	NO_2	For every 25 μg/m^3 increase in NO2 Atherosclerosis – Not evidence available. Arterial stiffness: Increase in cf-PWV and AIx Blood pressure and HT: Not associated with SBP, DBP, and HT.
	SO_2	For every 5 μg/m^3 increase in SO2 Atherosclerosis: Not evidence available. Arterial stiffness: Increase in cf-PWV Blood pressure and HT: Not associated with SBP, DBP, and HT.

Abbreviations: ABI: ankle-brachial index, ab-PWV: ankle-brachial pulse wave velocity, AIx: augmentation index, AP: augmentation pressure, cf-PWV: carotid-femoral pulse wave velocity, CAC: coronary artery calcification, CMIT: carotid intima-media thickness, DBP: diastolic blood pressure, HT: hypertension, NO_2:

nitrogen dioxide, PM: particulate matter, SBP: systolic blood pressure, SO_2: sulfur dioxide.

afterload, left ventricular hypertrophy, and fibrosis. Nevertheless, the comparability of these findings was limited due to high heterogeneity in the concentration and duration of the exposure to air pollutants, outcomes, and populations studied.

4. Urban pollutants and vascular ageing - does the gut microbiome play a role?

After AP inhalation, a small proportion is absorbed via the gastrointestinal tract [19] and might alter the structure and composition of the human GM, in terms of gene richness, biomass and diversity [11,20]. Regarding taxa composition, population studies have shown heterogeneous results. A systematic review found that AP has been related to the overgrowth of the phyla *Bacteroidetes, Deferribacterota*, and

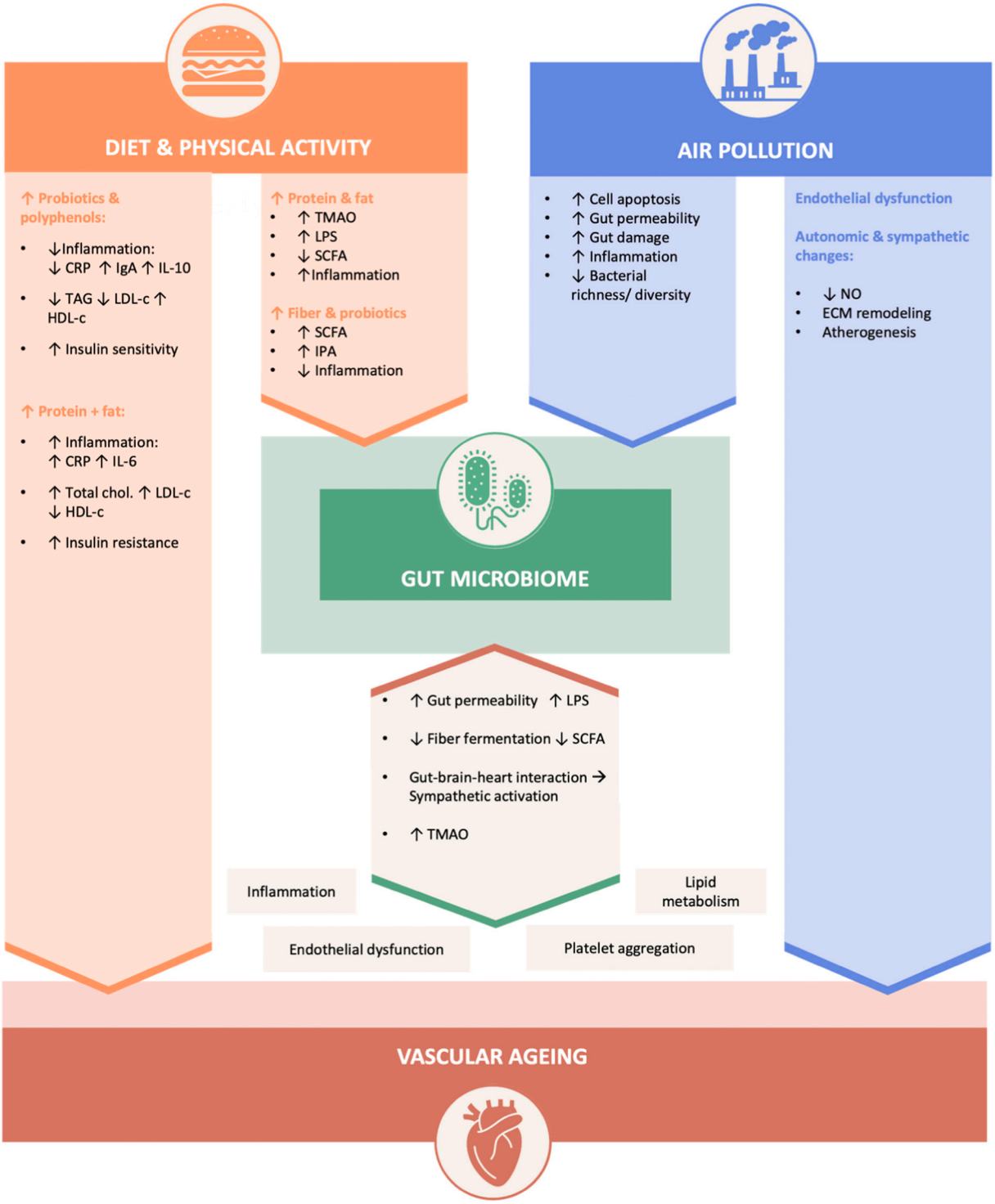

Fig. 2. A schematic representation illustrating the mechanisms through which urban lifestyles and physical-chemical risk factors (mainly air pollution) lead to vascular ageing, highlighting the potential mediating role of the gut microbiome.

Proteobacteria and the depletion of *Verrucomicriobiota* [20]. Only one study in humans reported that GM damage and inflammation could be the underlying mechanisms due to the high exposure to AP. On the other hand, in animal studies, long-term exposure consistently increases GM damage, inflammation, oxidative stress, and permeability [20].

Whether these pollution-induced alterations to GM impact VA are less clear [11], previous studies have proposed that $PM_{2.5}$ exposure may impair tryptophan metabolism, thus leading to GM dysbiosis. The subsequent production of central neurotransmitters, like serotonin, can activate the gut-brain axis [21], potentially explaining associated neurological and cardiovascular risks [22]. A study found that short-term inhalation of $PM_{2.5}$ led to shifts in GM composition, elevated serum hormone levels linked to the activation of both the hypothalamic-pituitary-adrenal (HPA) axis and gut-brain axis, as well as alterations in the nervous and cardiovascular systems. For the cardiovascular system, $PM_{2.5}$ was associated with an increase in CVD biomarkers, such as C-reactive protein, fetuin-A, a-acid glycoprotein, serum amyloid protein, haptoglobin, trimethylamine-N-oxide (TMAO), fasting blood glucose, and total cholesterol [22]. Drawing from these findings, the authors propose that $PM_{2.5}$ triggers GM dysbiosis, affecting tryptophan metabolism and activating the gut-brain axis, fostering changes in the nervous and cardiovascular systems, and contributing to VA.

5. How do urban lifestyles impact vascular ageing?

Living in urban environments often comes with a shift in lifestyle, such as sedentary behaviour, the paradox of overnutrition and obesity for some, and a lack of adequate diets for others [23]. Compelling evidence highlights key lifestyle factors—exercise, balanced diets, and controlled energy intake—as proven strategies for both preventing and optimising VA. Physical activity reduces age-related arterial and cardiac stiffness [24], while energy restriction counters cardiac changes linked to ageing [25]. Established diets like Dietary Approaches to Stop Hypertension (DASH) and the Mediterranean diet support healthy VA [26], with components such as fruits, vegetables, grains, nuts, legumes, fish, vegetable oils, and yoghurt linked to improve CVH [27]. Micronutrients also play a role, with higher calcium, magnesium, and potassium intake, coupled with lower sodium, correlate with enhanced CVH [26,28].

6. Urban lifestyles and vascular ageing - does the gut microbiome play a role?

6.1. Overview

Although the impact of diet on VA is extensively explored [29], its link to GM has recently piqued interest [30]. Dietary factors wield greater influence on GM traits than host genetics [31], highlighting how a shift to an urban lifestyle could in turn impact GM. Due to the higher cost of food in urban settings, poorer populations have diets that lack micronutrients and tend to be protein deficient, with increased consumption of animal-source foods, sugar, fats and oils, refined grains, and processed foods [23]. How this shift in diet could affect GM composition is outlined below. We also briefly outline how smoking and alcohol consumption, which tend to be more prevalent in urban settings [32,33], affect GM and could potentially accelerate the process of VA.

6.2. Diet and physical activity

Previous studies demonstrated that GM is an important mediator in the lower cardiometabolic risk related to a vegetarian diet. GM can be affected by plant-based diets through alterations in bacteria composition, for instance, increases in *Prevotella* and decreases in *Trimethylamine* (TMA). In addition, it is demonstrated that the Mediterranean diet may reduce TMAO and increase short-chain fatty acid (SCFA) production, and therefore decrease the risk of CVD [34] (Fig. 2). Whereas diets rich in animal-protein sources can increase CVD through biomolecules containing a TMA and phenylalanine [35]. Current evidence also suggests that some dietary factors may influence the abundance of *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*, which have been linked to CVD [36]. In addition, the intake of probiotics seems to have a role in reducing the risk of chronic diseases, including CVD through increasing the growth of beneficial bacteria and normal intestinal flora [37].

Some evidence has shown that exercise can decrease lipopolysaccharides (LPS) -induced systemic inflammation [38]. Moreover, a prospective study reported an inverse association between the levels of physical activity and TMAO levels among patients with type 2 diabetes [35].

6.3. Smoking and alcohol intake

High alcohol consumption, smoking, and second-hand tobacco smoke have been associated with CVD [6]. Emerging evidence suggests that smoking-associated dysbiosis alters the crosstalk of the gut-brain axis, contributing to VA [39]. It is demonstrated that cigarette smoking plays a role in promoting vulnerable plaque formation by interfering with the production of GM sphingolipid and regulating the levels of host sphingolipid [40]. Consequently, impaired insulin secretion, increased oxidative stress, boosted plaque inflammation and vascular smooth muscle cell apoptosis accelerate endothelial dysfunction and atherosclerosis [40]. Other potential mechanisms related to smoking-induced GM alterations include the introduction of cigarette-borne bacteria, increased biofilm formation, immune homeostasis disruptions, and raised oxygen tension [41]. Exposure to second-hand tobacco smoke in urban places has been shown to affect VA as smoking [42]. Whether these effects extend to the GM, remains to be researched.

On the other hand, alcohol can alter GM composition with an increase in Gram-negative bacteria [43]. Previous studies proposed the main role of corticotropin-releasing factor (CRF) and its receptors (CRFR1 and CRFR2) in the pathophysiological mechanism of leaky gut development [44,45]. In addition, excessive alcohol intake causes GM dysbiosis with increased *Enterobacteriaceae* and reduced *Bacteroidetes phyla* and *Akkermansia* and *Faecalibacterium* [42]. This may impact VA through the mechanisms previously described such as gut-brain axis dysregulation, chronic inflammation, and oxidative stress; however, further research is required.

7. Is the gut microbiome a pathway to improve vascular ageing?

7.1. Overview

The role of GM in CVH and disease has received increasing attention over the past decades [47]. Recent evidence links GM dysbiosis with a higher risk of CVD [46,48–54], among other diseases [50,55]. Meta-analyses have shown that bacterial metabolites, such as TMAO, increase the risk of major adverse cardiovascular events [56] and mortality [56,57]. Furthermore, the depletion of *Bacteroidetes* and *Lachnospiraceae* and the overrepresentation of *Enterobacteriaceae*, *Lactobacillus*, and *Streptococcus* taxa were described in coronary artery disease pathways [58]. Many of these changes induce pro-atherogenic effects in endothelial cells and maintain the vicious cycle of vascular damage.

7.2. The associations and mechanisms behind the gut microbiome and vascular ageing markers

Despite the advances in molecular biology, genomics and bioinformatics, the mechanisms of microbial metabolism and its derivates on cardiovascular physiology are still unclear [47,50]. As a standardised definition of VA is lacking, most studies addressing the effect of GM focus on the most frequently used, yet isolated, measures of VA (i.e., elevated BP or HT, AS, and atherosclerosis). Table 2 shows the main

Table 2
Summary of selected studies evaluating the effect of the gut microbiota on vascular ageing markers.

Authors (year)	Study name (country)	Study design	Participants	Sequencing method	Outcome definition	GM composition[a]			Possible pathways involved
						Higher abundance	Lower abundance	Diversity	
Blood pressure and hypertension									
Louca et al. (2021) [48]	TwinsUK cohort (UK) PREDICT-1 (UK)	Population-based cohort Randomised clinical trial Case-control analysis	TwinsUK cohort: $n = 871$ women (397 cases and 474 controls), age: 56 ± 11.3 y PREDICT-1: $n =$ 448 women (57 cases and 391 controls), age: 44.8 ± 12.1 y	16S	Systolic and diastolic BP: mean of 2 measurements. Cases: <60 y, SBP ≥140 mmHg, or DBP ≥90 mmHg, or antihypertensive medication, or started using before 60 y. Controls: if age > 50 y, SBP ≤120 mmHg and DBP ≤80 mmHg, and not on BP-lowering medication, or if age 50, SBP ≤115 mmHg and DBP ≤80 mmHg and not on BP-lowering medication	Erysipelotrichaceae UCG − 003	Ruminiclostridium 6	Significantly lower α-diversity Significantly higher β-diversity	*Ruminiclostridium* is involved in 84 pathways mostly related to metabolism (tryptophan, thiamine) ↑ Erysipelotrichacea increases systemic inflammation, cholesterol levels
Li et al. (2023) [59]	China	Mendelian randomisation	GWAS of HTN from the UK Biobank: 54,358 cases and 408,652 controls	16S	Cases: essential (primary) HTN (ICD-10 code I10) Controls: individuals without primary HTN or any other hypertensive disorder	• Eubacteriumxylanophilum • Eisenbergiella • Lachnospiraceae Risk factors (two-sample MR): • Alcaligenacea • Clostridiuminnocuum • Eubacteriumcoprostanoligenes • Eubacteriumfissicatena • Anaerostipes • LachnospiraceaeFCS020	• Alistipes • Bilophil • Butyricimonas • Phascolarctobacterium Protective factors (two-sample MR): • ClostridialesvadinBB60 • Allisonella • Parabacteroides • Phascolarctobacterium • Senegalimassilia	NR	NR
Gaundal et al. (2022) [51]	Norway	Cross-sectional study	$n = 49$ healthy individuals, mean age: 35.6 ± 13.1 y, women: 76 %	16S	Systolic and diastolic BP: mean of 2 measurements.	• *Dialister invisus* • *Megasphaera micronuciformis*	• Lactobacillus spp. • *Bacteroides stercoris* • Bacteroides spp. • Bacilli • *Eubacterium biforme* • *Eubacterium rectale* • Streptococcus spp. 2	NR	↓ *Lactobacillus* spp. might increase systemic inflammation, endothelial dysfunction, and salt sensitivity
Palmu et al. (2020) [52]	FINRISK (Finland)	Population-based cohort (cross-sectional analysis)	$n = 6953$, mean age: 49.2 ± 12.88 y, women: 54.9 % Comorbidities: HTN: 47.3 %, DT2: 5.6 %	Shotgun	Systolic and diastolic BP: mean of 2 measurements. HT: SBP ≥140 mmHg, DBP ≥90 mmHg, or antihypertensive medication	Acidaminococcus, Actinomyces, Anaerostipes, Bacteroides, Blautia, Cellulomonas, Clostridioides, Collinsella, Coprococcus, Desulfovibrio, Dialister, Dielma, Dorea, Eisenbergiella, Enorma, Enterobacter, Erysipelatoclostridium, Faecalitalea, Holdemania, Intestinibacter, Lactococcus, Megasphaera, Mitsuokella, Paraprevotella, Phascolarctobacterium, Ruthenibacterium, Sanguibacteroides, Sutterella, Turicibacter	• Lactobacillus spp. • Adlercreutzia • Alloprevotella • Anaerotruncus • Coprobacillus • Faecalicoccus • Fournierella • Hungatella • Parasutterella • Prevotella • Sellimonas • Senegalimassilia	Lower α-diversity (not statistically significant in multivariable models)	↑ *Firmicutes* increase TMAO ↓ *Lactobacillus* spp. might increase systemic inflammation, endothelial dysfunction, and salt sensitivity

(*continued on next page*)

Table 2 (*continued*)

Authors (year)	Study name (country)	Study design	Participants	Sequencing method	Outcome definition	GM composition[a]			Possible pathways involved
						Higher abundance	Lower abundance	Diversity	
							• Solobacterium • Tyzzerella		
Takagi et al. (2020) [49]	Japan		All: $n = 239$, median age: 68 y, women: 53 % HTN: $n = 97$, mean, median age: 69 y, women: 49 % Control: $n = 54$, mean, median age: 65.5 y, women: 61 % The remaining 258 individuals were assigned to the hyperlipidemia ($n = 96$) and T2D ($n = 162$) groups, respectively	16S	HT: SBP ≥140 mmHg or DBP ≥90 mmHg, or antihypertensive medication	• Actinobacteria • Collinsella	Bacteroidetes	NR	↑ Collinsella might impair lipid metabolism
Verhaar et al. (2020) [53]	HELIUS (Netherlands)	Population-based cohort (cross-sectional analysis)	$n = 4672$, mean age: 49.8 ± 11.7 y, women: 52 % Comorbidities: HTN: 41.5 % DT2: 10.9 %	16S	Systolic and diastolic BP: mean of 2 measurements. HT: SBP >140 mmHg or DBP >90 mmHg, or self-reported use of antihypertensive medication	Streptococcus	• Roseburia spp. • Clostridium spp. • Romboutsia spp. • Ruminococcaceae spp. • Enterorhabdus	Significantly lower α-diversity	↓ *Roseburia* and *Clostridium* decrease butyrate producers and down-regulate anti-inflammatory properties
Sun et al. (2019) [63]	CARDIA (US)	Population-based cohort (cross-sectional analysis)	$n = 529$, mean age: 55.3 ± 3.4 y, women: 53.9 % Comorbidities: HTN: 35.1 % DT2: 12.4 %	16S	Systolic and diastolic BP: mean of 2 measurements. HT: SBP ≥140 mmHg or DBP ≥90 mmHg, or antihypertensive medication	• Anaerovorax • Butyricicoccus • Cellulosibacter • Clostridium IV • Methanobrevibacter • Mogibacterium • Oscillibacter • Oxalobacter • Papillobacter • Sporobacter • Vampirovibri	• Anaeroglobu • Atopobium • Lactobacillus • Megaspheara • Pseudocitrobacter • Rothia • Robinsoniella	Significantly lower α-diversity Significantly higher β-diversity	↓ *Lactobacillus* spp. might increase systemic inflammation, endothelial dysfunction, and salt sensitivity
Li et al. (2019) [60]	China	Case-control study	NH: $n = 63$, mean age: 58.4 ± 10.2 y, women: 44 % AH: $n = 104$, mean age: 59.8 ± 9.3 y, women: 52 % HLD: $n = 26$, mean age: 56.7 ± 10 y, women: 46 %	16S	Systolic and diastolic BP: mean of 3 measurements. HT: SBP ≥140 mmHg or DBP ≥90 mmHg, or antihypertensive medication	• Lactococcus • Alistipes • Subdoligranulum • Prevotella	• Faecalibacterium • Bifidobacterium	NR	↑*Prevotella* increase inflammatory response

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Table 2 (*continued*)

Authors (year)	Study name (country)	Study design	Participants	Sequencing method	Outcome definition	GM composition[a]			Possible pathways involved
						Higher abundance	Lower abundance	Diversity	
			Control: $n = 42$, mean age: 59.3 ± 9.2 y, women: 60 %						
Jackson et al. (2018) [62]	TwinsUK cohort (UK)	Population-based cohort (cross-sectional analysis)	$n = 2737$, mean age: 60 ± 12 y, women: 89 %	16S	HT: self-report or antihypertensive medication	• Lactobacillaceae • Streptococcaceae	• Anaeroplasmataceae • Christensenellaceae • Clostridia • Dehalobacteriaceae • Mollicutes • Oxalobacteraceae • Peptococcaceae • Rikenellaceae	Lower α-diversity	↑ *Streptococcus* ➔ probably related with atherogenic processes
Yan et al. (2017) [61]	China	Case-control study	Cases: n = 60, mean age: 57 ± 9.6 y, women: 42 % Controls: $n = 60$, mean age: 56 ± 8.6 y, women: 47 %	Shotgun	Cases: SBP ≥140 mmHg and DBP ≥90 mmHg Controls: SBP ≤120 mmHg and DBP ≤80 mmHg. Matched by gender, age, and body weight.	• Klebsiella • Clostridium • Streptococcus • Parabacteroides • Eggerthella • Salmonella	• Faecalibacterium • Roseburia • Synergistetes	Significantly lower α-diversity and Shannon index	↑ Klebsiella, Clostridium, Streptococcus increase choline degradation ↓ SCFA ↑ *Streptococcus* ➔ probably related with atherogenic processes ↓ *Faecalibacterium and Roseburia* decrease SCFA production in colon
Atherosclerosis									
Wang et al. (2022) [75]	Women's Interagency HIV Study – WIHS (US) Multicenter AIDS Cohort Study – MACS (US)	Cross-sectional (WIHS) Longitudinal (WIHS + MACS)	Cross-sectional: $n = 361$, median age (IQR): 55 y (49–60), only women Longitudinal: $n = 737$, mean age: 57 ± 9.6 y, women: 54 %, median follow-up: 7 y	Cross-sectional: 16S Longitudinal: Metabolomic/ lipidomic profiling	Carotid artery plaque: localised intima-media thickness of >1.5 mm in any of the 8 carotid locations (High-resolution B-mode carotid ultrasound)	• Fusobacterium • Proteus	• Odoribacter • Adlercreutzia	No significant differences in α and β diversities	↑ *Fusobacterium* and *Proteus* change lipid metabolism and increase endothelial cell activation ↓ *Odoribacter* decrease butyrate production ➔ pro-inflammatory effect
Zhu et al. (2022) [77]	Taizhou Imaging Study – TIS (China)	Cross-sectional analysis (baseline of a population-based cohort)	$n = 569$, mean age: 59.8 ± 2.9 y, women: 57.3 % Comorbidities: HTN: 56.9 % DT2: 11.6 %	Shotgun	Subclinical CAS: CIMT >0.9 mm in either left or right common carotid artery	• Libanicoccus • Enterococcus • Methanobrevibacter • Helicobacter • Turicibacter	• Faecalicatena • Alistipes • Acinetobacter • Oligella	NR	↑ *Libanicoccus* increase gut permeability and inflammation ↓ *Faecalicatena* decrease SCFA production ➔ pro-inflammatory effect
Chen et al. (2021) [74]	China	Case-control study	Cases: $n = 31$, mean age: 51.32 ± 6.73 y, women: 39 %	Shotgun	Cases (CAS): left, right or bilateral common carotid artery or right subclavian artery atherosclerotic plaque	• *Bacteroides eggerthii* • *Escherichia coli* • *Klebsiella pneumoniae*	• Parabacteroides unclassified • *Prevotella copri*, • Bacteroides sp. 3_1_19	No significant differences in α and β diversities	↑ *Escherichia coli,* and *Klebsiella pneumoniae* increase low-grade inflammation via LPS metabolism

(*continued on next page*)

Table 2 (*continued*)

Authors (year)	Study name (country)	Study design	Participants	Sequencing method	Outcome definition	GM composition[a]			Possible pathways involved
						Higher abundance	Lower abundance	Diversity	
			Controls: $n = 51$, mean age: 48.49 ± 6.17 y, women: 49 %		formation (Color Doppler ultrasound). Controls: absence of abnormalities in the bilateral common, internal, and external carotid arteries, vertebral and subclavian arteries. Matched by age and sex.		• *Haemophilus parainfluenzae*		
Jie et al. (2017) [54]	China	Case-control study	Cases: $n = 218$, mean age: 61 y, women: 24 % Controls: $n = 187$, mean age: 60 y, women: 59 %	Shotgun	ACVD: ≥50 % stenosis in one or more vessels (coronary angiography)	• Enterobacteriaceae (*Escherichia coli*, Klebsiella spp., and *Enterobacter aerogenes*) • *Ruminococcus gnavus* • *Eggerthella lenta*	• *Roseburia intestinalis* • Faecalibacterium cf. prausnitzii, • Bacteroides spp. • *Prevotella copri* • *Alistipes shahii*	No significant difference in α diversity	↑ *Enterobacteriaceae* reduce glycans metabolism ↓ *Faecalibacterium and Roseburia* decrease SCFA production in colon
Arterial stiffness									
Li et al. (2023) [78]	Kailuan cohort (China)	Prospective population-based cohort (longitudinal analysis)	n = 96, mean age: 52.85 ± 6.5 y, women: 14 %, mean follow-up: 2.6 y	Shotgun	AS: ba-PWV ≥1.400 cm/s	• Escherichia • Shigella • Ruegeria	Desulfovibrio, Leptotrichia, Shewanella, Comamonas, Aquimarina, Spirosoma, Cytophaga, Tenacibaculum, Coraliomargarita, Desulfatibacillum, Leadbetterella, Geobacter, Anaerobiospirillum, and Flexibacter	No significant differences in α and β diversities	↑ Escherichia, Shigella, and Ruegeria increase inflammation
Menni et al. (2018) [76]	TwinsUK cohort (UK)	Population-based cohort (cross-sectional analysis)	$n = 617$, mean age: 61.42 ± 7.34 y, only women	16S	AS: cf-PWV (SphygmoCor system)	NR	• Ruminococcaceae • Rikenellaceae • Clostridiaceae • *Collinsella aerofaciens* • Barnesiellaceae • Clostridiaceae • Odoribacter	Significantly lower α-diversity	↓ *Ruminococcaceae* decrease butyrate and increase inflammatory cytokines and endothelial dysfunction

Abbreviations: ACVD: atherosclerotic cardiovascular disease, AH: hypertensive patients undergoing anti-hypertensive treatment, AS: arterial stiffness, ba-PWV: brachial-ankle pulse wave velocity, CAS: carotid atherosclerosis, cf-PWV: carotid-femoral pulse wave velocity, DBP: diastolic blood pressure, HLD: people with normal BP but with hyperlipidemia, HT: hypertension, LPS: lipopolysaccharides, NH: hypertensive patients with treatment-naive hypertension, NR: not reported, MR: Mendelian randomisation, SBP: systolic blood pressure, SCFA: short-chain fatty acids, TMAO: trimethylamine-N-oxide.

[a] Changes in gut microbiota composition when comparing cases vs controls or higher vs lower blood pressure, pulse wave velocity, or atherosclerosis markers.

findings from selected studies evaluating this association.

As expected, most evidence relates to BP or HT [46,48,49,51–53,59–63] and is highly heterogeneous. Alpha diversity was inversely associated with higher BP or HT [46,48,52,61,63,64], whereas the enrichment of gram-negative bacteria such as *Prevotella* [60], *Klebsiella* [61], and *Parabacteroides* [61] was consistently described. These bacteria promote gut permeability and LPS translocation into the bloodstream, activating pro-inflammatory cytokines that increase gut permeability in return [65,66] (Fig. 2).

This profile contrasts with the depletion of SCFAs (particularly butyrate) producers: mainly *Faecalibacterium* [60,61], *Roseburia* [53,61], *and Ruminococcaceae* [53]. SCFAs are produced through dietary fibre fermentation and have protective cardiovascular effects by reducing inflammation and improving endothelial function [67–72]. Furthermore, they indirectly participate in the LPS pathway and have a role in sympathetic activation by the gut-brain axis [65]. Finally, a lower abundance of *Lactobacillus* spp. was consistent across many studies [51,52,63]. A recent meta-analysis including 23 clinical trials showed that supplementation with several *Lactobacillus* spp. significantly lowered BP compared to a placebo [73], however several of the studies had small sample sizes which were more likely to overestimate the treatment effect.

Regarding AS and atherosclerosis, most studies did not show significant changes in alpha diversity [54,74,75], except for one study conducted in women, which identified a negative association with cf-PWV [76]. Interestingly, Zhu et al. [77] reported that GM explained 16.5 % of the mediation effect of lifestyle on the pathogenesis of carotid atherosclerosis, supporting the potential role of GM-modulating interventions.

GM in people with AS and atherosclerosis was enriched with *Enterobacteriaceae*, including *Escherichia* [54,74,78] and *Klebsiella* [54,74], whereas *Faecalbacterium* [54], *Roseburia* [54], and *Alistipes* [54,77] were underrepresented. These changes might upregulate inflammation due to high gut permeability and LPS, which contrast with lower plasma SCFAs.

TMAO regulation, bile acid metabolism, and direct vessel infiltration of microbiota have been proposed as key components in inflammation, hyperlipidemia, and thrombosis [65,66,79]. Elevated TMAO levels increase the risk of atherosclerosis and CVD, as they promote inflammation, impair cholesterol metabolism, and induce platelet hyperreactivity [56,57,80]. Additionally, dysbiosis can lead to altered bile acid metabolism, contributing to abnormal lipid profiles, and thus increasing the risk of atherosclerosis and CVD [67–72].

Lastly, bacterial DNA in atherosclerotic plaques [81] suggests a microbial environment originated either by direct vessel infiltration or distant infections [65]. This mechanism could be associated with an auto-immune response that promotes low-grade inflammation [82–84].

8. Discussion and future directions: towards precision prevention at individual and population levels

8.1. Summary

There is extensive research demonstrating the negative impacts of urban risk factors, such as AP and lifestyle, on VA and CVD [5]. The current review expanded this field by exploring the role of GM within this relationship, highlighting multiple mechanisms and pathways that may account for the association (Fig. 2). Environmental factors exert a dominant influence over genetics in initiating processes that shape GM, which also participates in VA, highlighting the importance of the exposome framework within this context. On a physical-chemical level, $PM_{2.5}$ appears to be the most detrimental to GM and VA, whilst understanding lifestyle participation in this association is more complex. Below we discuss how these factors may interact with other components of the urban exposome, suggesting entry points for research and interventions.

8.2. Two cosmoses, one universe: the interconnection of the microbiome

The current review has focused predominantly on physical-chemical elements and lifestyle factors in urban settings. However, the surrounding urban ecosystem and social structure play an important role too. Our microbiome makeup is largely influenced by our social and biological environment [8,85,86], despite being seeded at birth through maternal transmission [86]. We inherit only 6.6 % of our GM, whereas approximately 48.6 % of the variance is explained through cohabitation [85]. Other research estimates that we share 12 % of our GM with cohabitants [86]. This is drastic, considering we share almost 0 % of our microbiome with unrelated individuals in separate populations [86]. Our biological ecosystem also plays a role. In urban environments, AP, low soil diversity, and lack of green spaces lead to environmental microbial dysbiosis, which in turn has an impact on our own microbial makeup [8]. Urban lifestyles, such as sedentary behaviour and a poor diet could exacerbate these effects [13].

Given the high transmissibility of the microbiome, urban-induced microbial dysbiosis could be transmitted to those in the community, particularly in densely populated areas [86]. This concept challenges the notion of NCDs, suggesting that CVD could be shared via microbiome transmission [87]. This effect may be more prevalent in poorer communities, as those with lower incomes tend to have reduced access to adequate food and live in areas with high pollution, high population density, and fewer green spaces [23]. This might explain why socioeconomic factors, such as monthly income and neighbourhood income, are also associated with a healthy GM [85].

Taken together, this research reflects the rich and complex universe of the microbiome (Fig. 1). In this review, we focused predominantly on GM, inherently making a distinction between the internal and external microbiome. However, the microbiome does not recognise this boundary and readily crosses the human barrier, interacting with the abundant and diverse microbiome in our ecosystem [8,85,86]. The tools offered by the exposome approach may eventually be able to capture these subtle environmental exposures and improve our understanding of GM transmission and VA.

8.3. A paradigm shift in research and public health: moving towards an exposome approach

The association between urbanisation and GM might be a turning point in designing more effective preventive strategies to tackle the burden of CVD and its impact at all levels. By implementing a comprehensive and holistic framework with different layers at different life points, research, clinical practice, and policies can truly move forward to more effective prevention, diagnosis, and treatment of CVD. Despite the complexity of unravelling the interactions between ecosystems, lifestyle, social sphere, and physiological responses over the life span, the methods pioneered by the exposome approach are the most feasible path to incorporate these different environmental risk factors [3,4]. Promising methods include geospatial modelling, to measure various exposures, and network science and artificial intelligence models to analyse this complex data.

Using the exposome framework to study GM can help identify potential targets for intervention in the context of VA. While our genes are difficult to modify, our environment is more susceptible to change. Fortunately, this is what our GM is sensitive to [8,85,86], highlighting the importance of our lifestyle choices in buffering against the impacts of urbanisation. GM is modulated primarily by food intake and can be promoted by following healthy diets (e.g., vegetarian and Mediterranean diets) [34]. In addition, classic probiotic supplementation (such as *Lactobacilli* or *Bifidobacteria*) and fermented foods could be a strategy to mitigate urban risk factors by increasing GM diversity and preventing VA [37]. Emerging animal research into next-generation probiotics (such as *Faecalibacterium Prausnitzii* or *Desulfovibro piger*) also shows promise for butyrate production which has anti-inflammatory properties

and promotes intestinal homeostasis [88].

Moreover, emerging evidence demonstrates that antioxidant-rich diets and supplements can combat the oxidative stress induced by AP, with some promise in preventing and reversing its effect on VA [89]. Seeking out green spaces provides an opportunity for physical activity, social cohesion, and recovery from physiological stress within an environment with less air pollution, noise, and heat [13], which is beneficial for GM composition [85] and VA [5]. Interestingly, even if green spaces are limited, the positive effects of physical exercise outweigh the harmful effects of AP on VA [90].

The exposome approach can help us disentangle these complex environmental interactions and inform policymaking in the quest for tailored public health. As mentioned above, urbanisation may exacerbate the inequalities between the rich and poor, with subsequent impacts on health and disease [23]. A focus on AP reduction and green space development may be particularly promising in over-populated and poorer urban communities. This socioeconomic inequality is also seen on a larger scale, with low-middle-income countries being neglected in pollution research despite being more exposed [12].

8.4. *Future directions*

Despite the growing evidence and the advances in research designs, technologies, and analytical approaches, some challenges remain (Table 3). Although evidence on the effect of AP on VA and CVD [15] is more robust, longitudinal studies exploring emerging pollutants like novel insecticides, herbicides, and pharmaceutical waste are necessary [12]. Also, they must include the additive impact of co-occurring pollutants and environmental stressors, such as a lack of green spaces, noise, and light pollution [12,13], which may help identify how it impacts GM. Research should also be more inclusive by targeting underrepresented groups, such as people living in low-middle income countries and ethnic minorities, in which the impact of environmental pollutants and urbanisation-induced lifestyle changes could be worse [12].

As a limitation of this review, some urban risk factors which are likely to interact with GM and VA are not discussed here. For example, contamination of foodstuff in urban settings is ripe and undoubtedly related to GM dysbiosis. In addition, non-chemical pollution, such as light and noise pollution, may contribute to poor sleep, which in turn may interact with poor mental health that results from the burden of urban stressors. Mental illness and experiences of chronic stress may activate the HPA axis, which has been shown to affect VA and GM markers via the gut-brain axis [22]. Supplementary Fig. 1 provides an overview of which environmental factors were included in the review and which factors may be relevant and require further investigation.

8.5. *Improving our surroundings means improving our health*

The rise in global urbanisation poses a threat to both internal and external microbiomes, which are vital for human health due to their significant transmission potential. This interconnectedness underscores the need for a holistic approach to address VA and other NCDs. Compassion for the environment and those around will benefit the entire living planet as well as individuals' health and well-being. Prioritising global and planetary health in research and policy agendas is essential and demands further emphasis. Protecting the microbiome in the environment involves safeguarding green spaces and reducing pollution, which will also benefit the urban poor who might be more vulnerable to such risk factors. On an individual level, promoting healthy decisions by embracing biodiversity and physical activity can counteract noxious urban effects. To progress in this field, future endeavours should consider the interaction between these intrinsic and extrinsic factors to promote human, community, and planetary health; none of these acts in isolation.

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Table 3
Unanswered challenges in the effect of urban risk factors on vascular ageing mediated by the gut microbiome.

	Gaps and limitations	Future directions
Urban risk factors	**Vascular ageing** Heterogeneity in the measurement of the exposures (duration and concentration) Lack of confounding control	Prospective studies using a pollutome approach Inclusion of specific cellular components of inflammation Life-course approach (trajectories) Better control for confounders: age, sex, dietary intake, BMI.
	Gut microbiome Most studies using in vivo and in vitro models Short and long-term exposure in specific AP Lack of confounding control	Observational studies in general population or RCT with longer follow-up Prospective studies using a pollutome approach ➔ Interactions between AP components, ecological microbiome, and internal microbiome (not only GM) Better control for confounders: age, sex, dietary intake, BMI, medications.
Gut microbiome	**Vascular ageing** Evaluation of isolated VA markers Lack of integration with other omics data Lack of consensus regarding quality control, methodology, and pipelines Most studies are cross-sectional Lack of confounding control	Standardised and comprehensive definition of VA Multi-omics approach ➔ identify the impact of specific species/strains and metabolites on VA Interaction between microbiome universes: gut, oral, lung, vaginal Longitudinal studies including repetitive measures of GM and VA Better control for key confounders: age, sex, ethnicity, BMI, dietary intake, medications, other metabolites

Abbreviations: AP: air pollution, BMI: body mass index, VA: vascular ageing, GM: gut microbiome, RCT: randomised control trial.

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Declaration of competing interest

GG works for BioGaia AB, a probiotic company, and TM is the co-founder of Epistudia, an online platform for evidence synthesis; the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential competing interest. The authors declare no other competing interests regarding the research, authorship, or publication of this article.

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