REVIEW

Exposomes and metabolic health through a physical activity lens: a narrative review

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Abstract

In this narrative review, we provide an overview of the role of physical activity as part of differing exposomes (our combined non-genetic exposures from conception onwards) and environmental influences on metabolic health. We discuss 'beneficial' exposomes (green/natural outdoor spaces, sun exposure, healthy diets and features of built environments) that could synergise with physical activity to prevent metabolic dysfunction, particularly that related to lifestyle diseases of obesity, type 2 diabetes and metabolic syndrome. Physical activity may also reduce the capacity of some adverse exposomes, specifically those with significant levels of air pollution, to contribute towards metabolic dysfunction. Other exposomes, such as those experienced during pandemics (including COVID-19), potentially limit opportunities for physical activity, and there may be unexpected combined effects of physical activity with other infections (e.g. adenovirus-36) on metabolic health. Finally, we discuss how environments could be better optimised to create exposomes that promote the health benefits of physical activity and likely future directions of this research field.

Key Words

- ▶ physical activity
- ▶ exercise
- ▶ exposome
- ▶ metabolic health

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Introduction

Physical activity is essential for good health

The beneficial effects of physical activity are clear for metabolic and overall health. It is advocated by the World Health Organisation, International Society for Physical Activity and Health, Obesity Society and many agencies and government health bodies around the world as an important means of reducing the risk of developing metabolic dysfunction. Indeed, physical activity reduces the risk of developing at least 35 chronic diseases (Booth *et al.* 2012), including, type 2 diabetes, non-alcoholic fatty liver disease, cardiovascular disease, as well as some cancers, while also contributing towards bone mineral density, brain and mental health, and mobility (McGee & Hargreaves 2020, Thyfault & Bergouignan 2020). Many

of these chronic diseases are underpinned by metabolic dysfunction and are increasing in prevalence in countries across the world. Therefore, developing targeted and better-defined lifestyle approaches that more effectively prevent or treat the harms of metabolic dysfunction are warranted. Advice to increase physical activity levels is routinely given as part of lifestyle approaches towards reducing metabolic dysfunction. Even relatively small amounts of activity (e.g. >3500 steps/day) may be protective (Fretts *et al.* 2012), although many public health and health promotion programs promote much more (i.e. ≥10,000 steps/day). Physical activity regulates insulin sensitivity (how sensitive the body is to insulin for control of blood glucose) and systematic metabolism via acute and chronic adaptations, which are underpinned

by inter-tissue communications that prevent metabolic derangement (Thyfault & Bergouignan 2020). Well-described adaptations by skeletal muscle are likely complemented by adaptations in many tissues (including liver, heart, pancreas, gut and brain) controlled by the interplay of potentially thousands of exercise-induced mediators to prevent excessive inflammation and oxidative stress and promote insulin signalling (McGee & Hargreaves 2020, Thyfault & Bergouignan 2020). In this review, we explore how differing environmental conditions and exposomes could modulate the capacity of physical activity to affect metabolic health.

Physical activity in differing environments

Determining how physical activity could be best tailored to treat chronic metabolic disease is an important research focus, with ongoing consideration of what are the best approaches, including exercise modality/type (e.g. resistance vs aerobic), intensity, frequency and duration and complementary nutritional approaches (McGee & Hargreaves 2020, Savikj & Zierath 2020). Where physical activity takes place is another important consideration. There is emerging evidence of the impact of environmental influences – including air pollutants (Li *et al.* 2019, Yang *et al.* 2020) and sun exposure (Gorman 2020) – on metabolic health. These exposures modulate metabolic health in differing directions, with harms described for air pollution, and some benefits for low-level (non-burning) sun exposure. Similar to physical activity, both exposures affect metabolic processes in a variety of tissues, acting through an array of interacting mediators that affect pro-inflammatory and oxidative stress pathways, in addition to other novel effects on liver lipid turnover and the gut microbiome (Li *et al.* 2019, Feng *et al.* 2020, Gorman 2020, Vogel *et al.* 2020). How these exposures – and their induced mediators – interplay with physical activity to affect metabolic health is yet to be fully defined, and further research is needed to determine the best conditions in which to undertake the exercise for prevention and treatment of metabolic dysfunction.

One increasingly important example of metabolic dysfunction is metabolic syndrome, a cluster of conditions (high blood pressure, high blood glucose, abdominal adiposity and hyperlipidaemia) that increase the risk of heart disease, stroke and type 2 diabetes (Grundy *et al.* 2004). Regular moderate-intensity physical activity is consistently associated with a lower prevalence of metabolic syndrome; however, higher intensity vigorous physical activity (and the associated increase

in cardiorespiratory fitness) may provide greater benefit (Churilla & Zoeller 2008, Zhang *et al.* 2017, Amirfaiz & Shahril 2019). There is little evidence for significant associations with light-intensity physical activity (Amirfaiz & Shahril 2019), yet increased sedentary time is positively associated with metabolic syndrome (Guinhouya *et al.* 2011, Amirfaiz & Shahril 2019). These associations appear to be similar in adults and youth (Guinhouya *et al.* 2011, Amirfaiz & Shahril 2019). Finally, physical activity is associated with a number of individuals (self-efficacy, motivation, intention and other related personal beliefs), social (support from family, friends, and work; wider community and organisational norms and practices) and physical (neighbourhood walkability, access to vegetation, high-quality parks and recreational facilities, aesthetics, crime and safety) environmental factors (Trost *et al.* 2002, Bauman *et al.* 2012) that could modulate the nature of its associations with metabolic dysfunction.

What are exposomes?

The exposome includes all environmental (i.e. non-genetic) exposures that are received by a person throughout their life, from conception onwards (Wild 2005). These accumulate and interact together with a person's genome to affect their health and development (Nieuwenhuijsen 2016). Characterisation of exposomes includes 'bottom-up' approaches, which attempt to measure the environment a person lives in, and 'top-down' approaches, which focus on measuring a person's direct exposures. This may be done through characterisation of metabolites present in blood (Rappaport 2011), and/or by dosimetry (e.g. actigraphy for physical activity; radiation dosimetry for sun exposure) (Drewnowski *et al.* 2020). Recent research, in particular, has focused on metabolomic (measurement of metabolites in a specimen) approaches to better understand the effects of exposomes on health (Rattray *et al.* 2018). These often provide information on the exposures, but not necessarily their sources (Rappaport 2011), especially those influenced by human behaviours. A good example of this is 25-hydroxyvitamin D, the metabolite used to determine vitamin D status and an important determinant of bone health (Bouillon *et al.* 2019). Levels of this metabolite are well-known to be influenced by sun exposure, vitamin D supplementation and diet; however, 25-hydroxyvitamin D levels are likely also influenced by ill health (Autier *et al.* 2014) and physical activity (Abboud *et al.* 2017, Sun *et al.* 2017, 2018). Using 25-hydroxyvitamin D as a proxy for sun exposure only, likely underestimates the

influence of other elements of the exposome. Therefore, environmental health studies that combine approaches that characterise both the environment a person lives in, and their personal exposures (merging metabolomics, genomics and dosimetry) are essential to define the best environments and means to promote optimal health.

The exposome and metabolic dysfunction

In addition to air pollution and sun exposure, environmental influences on metabolic health include factors that likely affect our capacity to undertake physical activity, such as walkability (how easy it is to walk in a given area), green space and other resources and elements (e.g. noise pollution, crime, safety) of the built environment, as well as weather and geography-related impacts (e.g. season, day length, altitude) (Dendup *et al.* 2018). Other risks include personalised exposures such as diet and intake of alcohol and caffeine, endocrine (metabolic) disruptors, physical inactivity and sedentary activities, social networks, lifestyles that affect circadian rhythm (e.g. shift work), socioeconomic status and education (Bhatnagar 2017, Bellou *et al.* 2018, Le Magueresse-Battistoni *et al.* 2018). Importantly, multiple methodological issues still impede our capacity to demonstrate causality in this space, with most investigations utilising cohort (longitudinal, cross-sectional) or ecological data. Similarly, how applicable findings collected to-date are for people living in different environments across the world is uncertain, as most have been reported from people living in high-income settings (reviewed by Dendup *et al.* 2018, DeFlorio-Barker *et al.* 2020).

Physical activity within exposomes and effects on metabolic health

In this narrative review, we apply a 'physical activity lens' to provide an overview of the impacts of physical activity on metabolic health in differing exposomes (and vice versa). Our intention was to provide a narrative review and perspective of this broad field, describing current research foci and highlighting possible new avenues of research. These include consideration of understudied topics, or unknown interactions between certain exposomes/elements within exposomes, with physical activity and metabolic health. A literature search was conducted on PubMed (until 1 August 2020) in which the following keywords were combined: (physical activity, exercise) AND (exposome) AND (addiction, air pollution,

alcohol, altitude, bad habits, beverage, built environment, clean air, cigarette, climate change, circadian, crime diet, diurnal, drug abuse, education, e-cig(arette), endocrine-disrupting chemical, fat, fire, fructose, gluten, global warming, green space, healthy diet, heat, humidity, latitude, light at night, Mediterranean diet, melatonin, opioid, poverty, prescription drug, prescription medicine, processed, recreation(al) drug, remote, rural, safety, salt, smoking, socioeconomic status, sugar, sun exposure, sweetened, temperature, tree, ultraviolet, unhealthy diet, urban, violence, volatile organic compounds, walkability OR water). For some searches, no articles were identified including combinations with the search terms/phrases: circadian, crime, diurnal, drug abuse, light at night, melatonin, opioid, prescription drug, recreation(al), safety, and violence. Overall, this search strategy yielded 36 publications in total, including 21 primary articles, and 15 reviews/other articles. All articles from these searches were reviewed, with 26 (17 primary research articles and 9 review articles) cited in this narrative review. Reasons for excluding the remaining 10 articles included: findings not specific to metabolic health (4 primary articles); and articles that did not provide insights specific to metabolic health and physical activity or referred to primary articles identified through the search conducted above (which were instead cited below) (6 reviews/other papers). Only papers published in English were included. Identified research was categorised into several themes including: (i) beneficial exposomes that promoted and/or had synergy with physical activity to improve metabolic health; (ii), harmful exposomes in which doing physical activity may affect metabolic function or may limit capacity to do physical activity; (iii) environmental determinants of exposomes that had effects on metabolic health that may be independent of physical activity; (iv), and exposures that may be risky or have uncertain or unknown interactions with physical activity (Fig. 1). Finally, we discuss issues around how environments can be better optimised to improve physical activity outcomes for metabolic health, and likely future directions of this field of research.

Physical activity as part of a 'beneficial' exposomes

Physical activity, green space and natural outdoor environments

Green spaces or natural outdoor environments (e.g. parklands, bushlands, open spaces, wetlands, rivers,

Figure 1

The impacts of physical activity on metabolic health in differing exposomes (and vice versa). Beneficial exposomes that promoted and/or could have synergy with physical activity to associate with improvements in metabolic health included: natural outdoor environments (green spaces) with little pollution; provision of walking and cycling infrastructure and physical activity facilities (e.g. swimming pools, gyms); capacity for low dose/safe sun exposure; and (access to) healthy diets. Harmful exposomes in which doing physical activity was associated with adverse impacts on metabolic function included: those with polluted environments (particularly air pollution); limited walkability or cycling infrastructure or access to physical activity facilities; and increased access to unhealthy foods (i.e. takeaway or fast foods). Environmental determinants of exposomes identified to be associated with metabolic health outcomes that could have effects on metabolic health independent of physical activity included: maternal and passive smoking; air and organic pollutants; alcohol intake; healthy diets; and living in densely populated areas. Finally, exposomes that may be risky or have uncertain or unknown interactions with physical activity included those that promote: immunosuppression and viral infections (including impacts of pandemic-induced social distancing and lockdowns); increased movement of transposable DNA elements (i.e. transposons); climate change and global warming; endocrine-disrupting chemicals; food contaminants; safety and violence; neglect; addiction and opioid use; and, societal value on sports participation by girls and women.

beaches) provide space for outdoor physical activity, with other proposed benefits for mental health, sleep, social contact, and reduced exposure to urban pollutants such as carbon dioxide (CO₂), particulate matter, noise and heat (Kumar *et al.* 2019). Potential risks from green space may include excessive sun exposure (e.g. skin cancer; although this can be prevented by tree canopies, shading and sun-protective behaviours), exposure to airborne allergens (e.g. pollen) and vector-borne diseases (e.g. those transmitted via ticks – Lyme disease) (Donaire-Gonzalez *et al.* 2019, Kumar *et al.* 2019, VanAcker *et al.* 2019). Other risks of undertaking physical activities, such as jogging, include that done in green spaces located within or in close proximity to urban areas with increased airborne particulate matter (Liu *et al.* 2019), or biogenic volatile organic compounds (e.g. isoprene), which are precursors to ground-level ozone and secondary organic aerosols (Salmond *et al.* 2016, Ren *et al.* 2017). For example, Californian children participating in outdoor team sports in areas of high ground-level ozone had an

increased relative risk of developing asthma (McConnell *et al.* 2002). That said, most health impact monitoring studies suggest that the benefits of physical activity in green spaces outweigh the potential costs of exposure to additional air pollution (Doorley *et al.* 2015, Mueller *et al.* 2015). In a study of pregnant women ($n = 167$) and children ($n = 183$) living in three European cities, a 'personalised monitoring kit' was used to characterise personal exposomes, and included measurement of physical activity (via accelerometer), exposure to UV radiation (via dosimeter), traffic noise (via smartphone) and air pollution (via two monitors; one measuring particulate matter 2.5 μm (PM_{2.5}) levels, the other black carbon) (Donaire-Gonzalez *et al.* 2019). Significant (but 'low strength'; $r < 0.3$) correlations between physical activity and the surrounding 'greenness' (normalised greenness vegetation index) or green space (time spent in natural outdoor environments) or UV dose received (but not pollutants) were observed in pregnant participants (Donaire-Gonzalez *et al.* 2019). These data suggest that

the physical activity done was associated with exposomes that had natural outdoor environments. This, in turn, may increase an individual's exposure to UV radiation, which may have additional metabolic benefits (Gorman 2020), although this needs to be balanced with the risks of excessive sun exposure. An important limitation of this study was its relatively small sample size.

Physical activity and sun exposure

Our recent pre-clinical studies point towards potentially metabolically beneficial synergies between physical activity and sun exposure (Allemann *et al.* 2020). We observed increased expression of mRNAs linked with thermogenesis (*Ucp1*), fatty acid synthesis (*FasN*) and insulin signalling (*Igf1*) in interscapular brown adipose tissue of mice exposed to non-burning UV radiation (1 kJ/m²) and allowed access to running wheels, compared to either treatment alone (Allemann *et al.* 2020). In other studies, we demonstrated that many of the metabolic benefits of UV radiation occurred through skin release of nitric oxide (Geldenhuys *et al.* 2014, Fleury *et al.* 2017, Dhamrait *et al.* 2020). This process is multi-phasic, involving keratinocytes and endothelial cells (Holliman *et al.* 2017), occurs in human skin (Liu *et al.* 2014) and may allow for sustained release of nitric oxide for improved physical performance in conjunction with dietary nitrate (Muggeridge *et al.* 2015). Exposure to UV radiation did not increase the distance run in mice fed a high-fat diet (Allemann *et al.* 2020). Furthermore, women with 'active sun exposure habits' had a 30% reduced risk of type 2 diabetes following adjustment for differences in physical activity levels (determined via questionnaire and adjusted for age, BMI, smoking) (Lindqvist *et al.* 2010), suggesting there are also beneficial effects of sun exposure independent of physical activity for metabolic health. These may include improvements in insulin sensitivity and reductions in adiposity, as observed previously in experimental mice fed a high-fat diet (Geldenhuys *et al.* 2014, Fleury *et al.* 2017, Dhamrait *et al.* 2020). Further research is necessary that measures both sun exposure and physical activity levels at a personal level, as well as other elements of the exposome, to better define their combined impacts on the metabolic health of humans.

Physical activity and diet

Physical activity and diet combined as lifestyle interventions to prevent and treat metabolic dysfunction are the subjects of much research. Indeed, the relationships

between physical activity and diet/nutrition are complex and controversial (Hughes 2014), influenced by the diversity of diet-related 'risk pathways' that range from satiety to the gut microbiome food quality and dietary patterns; determinants of dietary choice; food processing and preparation; and, use of supplements (Mozaffarian 2016, Drewnowski *et al.* 2020). For example, in an Italian study, increased levels of physical activity was observed in children ($n=178$) with 'normal' weight compared to children with overweight or obesity, with no difference in diet quality observed between these groups (De Giuseppe *et al.* 2020). The reader is directed to recent reviews that discuss how combining physical activity and diet to treat metabolic dysfunction may promote weight loss, reductions in liver fat, improvements to blood glucose control and fitness, and higher disease remission rates (e.g. for type 2 diabetes) (Aoyama & Shibata 2020, Magkos *et al.* 2020, Ross *et al.* 2020, Savikj & Zierath 2020). The Mediterranean diet, hypocaloric diet and/or diets that promote caloric restriction are common strategies that are often combined with an increasing physical activity levels as first-line therapy for many metabolic disorders (Pani *et al.* 2020, Ross *et al.* 2020). This combined approach has benefits for metabolic health that likely exceed either diet or physical activity interventions on their own (Ross *et al.* 2020). Other studies point to the speed at which changes in physical activity and diet may affect metabolic health. For example, substantial reductions in step count (limited to 1500 steps/day) combined with a high-caloric diet (+50% kcal) reduced insulin sensitivity after 3 days, and caused weight gain after 7 days in healthy young men (Knudsen *et al.* 2012). However, maintenance of the metabolic benefits of lifestyle interventions is difficult due to hunger and lack of post-meal satiety signals, affecting long-term compliance (Magkos *et al.* 2020). In addition, a number of individual and environmental factors influence short- and long-term physical activity behaviour change. These include a person's self-efficacy and motivation, physical activity/exercise history, skills and ability to participate in physical activity, and other health behaviours (Trost *et al.* 2002, Bauman *et al.* 2012). Environmental influences of physical activity behaviour change include perceived and actual access to required facilities, financial and time barriers as well as the level of social support (Dishman *et al.* 1985, Sherwood & Jeffery 2000, Amireault *et al.* 2013).

How to best combine physical activity and diet as lifestyle strategies to improve metabolic health is an industrious and controversial area of research. Factors that may be important include the types and balance of

macronutrient intake (i.e. fat, carbohydrate, protein), the nature of physical activity done (i.e. intensity, duration, type, frequency), the timing of activity relative to when meals are eaten, the influence of circadian rhythm, and how to provide advice that is best tailored to an individual's physiology and personal preferences (i.e. precision dietary (Magkos *et al.* 2020) and physical activity (Bulbul 2020) strategies). Savikj & Zierath (2020) recently reviewed the evidence around substrate availability provided through the diet and observed that low carbohydrate availability may force the use of stored lipids as fuel sources, promote mitochondrial biogenesis, and increase cardiovascular function and skeletal muscle oxidative capacity in athletes. Conversely, low-intensity exercise may improve glycaemic control post-prandially (after eating); however, there is limited knowledge of the impacts, and potential health risks around limiting substrate availability, or exercising after meals, in people with type 2 diabetes (Savikj & Zierath 2020). Other studies suggest that exercising in the morning before breakfast may promote long-lasting effects on fat oxidation, compared to exercise done after breakfast (reviewed by Aoyama & Shibata 2020).

Physical activity and the built environment

The built environment includes anthropogenic (human) structures, features and facilities in a given area. Elements of the built environment that may promote physical activity include its inherent walkability, the provision of physical activity destinations and resources (e.g. gymnasiums, swimming pools, sports fields), and playgrounds. These are often studied with other elements of the built environment, including type and number of food outlets, population density and socioeconomic status, street connectivity, land use mix, aesthetics and public transport infrastructure. For example, in a study of children ($n = 681$, 6–12 year olds) who were classified as living in one of four neighbourhood types (based upon park quality, street networks and connectivity (i.e. walkability), presence of supermarkets or fast food restaurants, and residential density), those living in 'less environmentally supportive' neighbourhood types had higher rates of overweight/obesity (Saelens *et al.* 2018). These less supportive neighbourhoods were less walkable, had fewer recreation facilities and access to lower-quality nutrition. In other studies, the number of physical activity resources (in given regions) was associated with reduced risk of insulin resistance after adjusting for differences in socioeconomic status (Auchincloss *et al.* 2008). Importantly, physical activity facilities (e.g. gyms,

swimming pools) may reduce obesity risk in areas with fewer green spaces and more takeaway stores (Mason *et al.* 2020).

Physical activity may limit metabolic dysfunction caused by adverse exposomes

Exposomes with air pollution may limit opportunities for physical activity

Around the world, air pollution varies from clean/'good' (e.g. $5 \mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ (Hobart, Australia) to dirty/'hazardous' (e.g. $500 \mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ (Cork, Ireland) (data obtained at <https://aqicn.org/>, 06:00 GMT, 31 August 2020). In a meta-analysis of 7 cohort studies, every unit ($\mu\text{g}/\text{m}^3$) increase in ambient $\text{PM}_{2.5}$ levels, increased the odds for physical inactivity by 1.1% (Lu *et al.* 2015, An *et al.* 2018b). These findings suggest that hazardous levels of air pollution may have substantial impacts on physical activity. Indeed, extreme levels of air pollution sometimes result in the cancellation of outdoor physical activities that would otherwise be undertaken by school students living in some Chinese cities (Dong *et al.* 2018). Experimental cycling studies suggest that a range of health outcomes are affected by exercising in conditions with poor air quality, with effects on: brain plasticity, respiration, heart rate, blood pressure, inflammation, thrombosis and coagulation, although findings are mixed (Lu *et al.* 2015, Giorgini *et al.* 2016, Hankey & Marshall 2017). Important factors regulating exposure to air pollutants for commuting cyclists likely includes the cycling route (i.e. proximity to roads and areas of industry) and level of exertion undertaken, as well as gender, time-of-day, and season (Shrestha *et al.* 2020). Detrimental effects on pulmonary and cardiovascular function as well as physical performance have been observed in athletes competing in the Olympic Games in locations with high levels of air pollution (Bos *et al.* 2014). Health impacts of air pollution are likely linked to increased intake (inhalation/ingestion) of particulate matter and ozone when exercising, due to increased ventilation rates (Bos *et al.* 2014, Dong *et al.* 2018, DeFlorio-Barker *et al.* 2020), reduced mucociliary clearance, increased breathing from the mouth and raised pulmonary diffusion capacity (Giorgini *et al.* 2016). Particulates may directly affect tissues inducing inflammation and oxidative stress, and/or indirectly causing systemic inflammation through the lungs, eyes and skin (Bos *et al.* 2014). Effects on brain health have been linked to brain-derived neurotrophic factor, an important myokine released into blood with exercise,

levels of which were suppressed when physical activity was done in a polluted room (Bos *et al.* 2011).

Health benefits of physical activity may offset risks of air pollution

Overall, trade-offs between physical activity and air pollution suggest that there are greater health benefits of shifting towards active forms of transport, which outweigh risks of increased exposure to air pollution (Giorgini *et al.* 2016, Hankey & Marshall 2017). This may be location-specific, with more research needed in regions where air pollution levels are extreme, such as that occurring in some Chinese cities (Lu *et al.* 2015), or in Australia during severe bushfire events (Bambrick *et al.* 2011). A further factor regulating the cost-benefit relationship of exercise and air pollution, includes consideration of the type of activity done, for example low impact activities (e.g. gardening) may be less protective when air pollution levels are high (Andersen *et al.* 2015). Furthermore, undertaking low impact activities in these conditions may have negative short-term health impacts, particularly in older individuals with lung disease (Sinharay *et al.* 2018) or those at-risk of heart disease (Giorgini *et al.* 2016). This may also be related to how low impact activities can be undertaken for longer periods of time, increasing exposure times, while high impact activities are often shorter in length, but substantially augment inhalation rates to potentially increase pollutant exposure across a shorter timeframe. Conversely, moderate-to-high intensity activities are likely beneficial for healthy people, even when concentrations of pollutants are high (DeFlorio-Barker *et al.* 2020).

Protective mechanistic pathways induced by physical activity likely involve epigenetic regulation of genes. For example, reduced DNA methylation of the *FOXP3* promoter (indicative of higher gene activity) was observed in buccal cells from 'active' compared to 'non-active' children who were exposed to high levels of black carbon (1200 ng/m³) in New York City (Lovinsky-Desir *et al.* 2017). This finding is of particular interest as *FOXP3* gene expression is highly correlated with the activity and function of regulatory T cells, which act to suppress inflammatory processes that promote insulin resistance (McLaughlin *et al.* 2017). In addition to those with pre-existing cardiometabolic dysfunction or lung conditions, other at-risk groups include children and adolescents, who have incomplete tissue development and different inhalation rates and body sizes compared to adults (Dong *et al.* 2018). Children are particularly vulnerable to the effects of air pollution for a variety of physiological and

behavioural reasons (Schwartz 2004). For example, they breathe faster than adults (Iliff & Lee 1952), their respiratory epithelium is more permeable (Bateson & Schwartz 2007), their breathing 'zones' are closer to the ground where certain pollutants are more common (Burtscher & Schüepf 2012) and they spend more time outdoors (Cohen Hubal *et al.* 2000). On a per kilogram of body mass basis, children breathe more air and have greater lung surface areas than adults (Poets *et al.* 1993, Arcus-Arth & Blaisdell 2007), facilitating particulate matter inhalation and deposition.

Identifying elements of the exposome which affect metabolic health independent of physical activity

Statistical approaches have been used to identify important and novel environmental determinants of metabolic health that are independent of physical activity. In the HELIX study of 1301 children (aged 6–11 years) in which data were combined from six European birth cohorts, maternal exposures in pregnancy (smoking), and childhood exposures (passive smoking, air pollutants, residence in densely populated areas, reduced facilities near schools) were associated with increased BMI (Vrijheid *et al.* 2020). Sensitivity analyses indicated little effect of physical activity (maternal or childhood) levels (measured via questionnaire and corrected using accelerometer data from a subset of participants) on these associations. Similarly, in a case-controlled study of older adults ($n = 1779$), increased incidence of type 2 diabetes was associated with baseline levels of persisting organic pollutants (e.g. poly-chlorinated biphenyls), after adjusting for physical activity (from questionnaire-derived data) and other factors (e.g. BMI, alcohol, smoking) (Wolf *et al.* 2019).

Physical activity is a key aspect of the 'Mediterranean lifestyle' which includes consumption of a largely plant-based diet (Tuttolomondo *et al.* 2019). In the PREDIMED study, increased adherence to Mediterranean diet ($n = 22,043$ adults in Greece) was associated with reduced deaths due to heart disease after controlling for physical activity (questionnaire-derived) amongst other factors (e.g. sex, smoking) (Trichopoulou *et al.* 2003). This analytical approach may also be useful for identifying underlying mechanisms. For example, alcohol intake (but not physical activity levels measured via questionnaire) was associated with the expression of an oxidative stress marker (DNA strand breaks) in lymphocytes isolated from

healthy older (>40-year-old) women ($n = 62$) (Goncalves Mota *et al.* 2017), although this study was limited by its relatively small sample size. Further limitations of these approaches are the frequent use of questionnaires to determine physical activity, which may sometimes be inaccurate, with over-reporting likely influenced by recall and/or social desirability biases, particularly for light or moderate-intensity activities (Strath *et al.* 2013). Even so, controlling for differences in physical activity (and other known modifiers) may provide evidence to help identify important and novel determinants of metabolic health that have effects independent of physical activity.

Potentially risky, uncertain and unknown interactions of exposomes with physical activity

Exercise-induced immunosuppression, chronic fatigue illnesses and viral infections

Excessive or 'arduous' levels of physical activity above recommended levels may compromise immune responses, particularly in athletes, and put individuals at increased risk for infection particularly of the upper respiratory tract (Simpson *et al.* 2020). This is a controversial area of research, with some hypothesising that it is more the stresses and interactions involved in preparing for and participating in competitions and high-performance events that compromises immunity (Simpson *et al.* 2020). Immune impacts of excessive exercise may include effects on innate pathways (e.g. natural killer cell function), adaptive processes (e.g. involving T and B cells) and increased risk for viral reactivation. Viral infections may also combine with physical activity in (other) unexpected ways to affect metabolic health. For example, infection with adenovirus-36 may prevent weight loss induced by exercise, but these exposures combined for more effective glycaemic control, mediated by improvements to mitochondrial numbers and their integrity in the liver (reviewed by Kim *et al.* 2020).

Viral infections may also limit our capacity to do physical activity, with COVID-19 (coronavirus disease of 2019)-related chronic fatigue illnesses anecdotally observed in 10% individuals ≥ 3 months after acute infection with SARS-CoV-2 (Williams *et al.* 2020). This is often now referred to as 'long COVID' and could be defined as symptoms (cardiovascular, pulmonary, neurological, psychological) that persist beyond 4 weeks of the initial illness (Datta *et al.* 2020). Viral-related chronic fatigue illnesses may potentially be exacerbated

by physical activity (Williams 2020), with declines in physical function and fitness persisting for up to 2 years post-initial infection with the related coronavirus, SARS-CoV (Rooney *et al.* 2020). Of additional relevance to metabolic health are the plausible links between viral infections, particularly those linked with chronic fatigue syndrome (Proal & Marshall 2018), and the development of insulin resistance (Zhao *et al.* 2012) and type 2 diabetes (Spadigam *et al.* 2016). Viruses associated with both chronic fatigue syndrome and insulin resistance include those with the capacity to establish long-term persistence, such as Epstein-Barr virus and cytomegalovirus (Proal & Marshall 2018). The metabolic effects of SARS-CoV-2 infection are yet-to-be fully realised, although there are well-described increased risks of severe COVID-19 for people with obesity, cardiovascular disease and type 2 diabetes (Li *et al.* 2020, Popkin *et al.* 2020, Xu *et al.* 2020), with glycaemic control measures likely reducing the impact of severe COVID-19 events (Marazuela *et al.* 2020).

Social distancing and isolation strategies used to combat the COVID-19 pandemic may also limit capacity for physical activity, with step-counts from smartphone accelerometers of people living in 187 countries reducing by >25%, 30 days after the COVID-19 pandemic was declared by the World Health Organisation (11 March 2020) (Tison *et al.* 2020). There are likely negative consequences and cumulative effects of the COVID-19 pandemic on physical activity with positive energy balances hypothesised due to reduced physical activity levels, and increased leisure-based screen time and consumption of unhealthy foods (Martinez-Ferran *et al.* 2020). It is still largely unknown how these factors combine with other elements of the exposome to affect metabolic health. For example, air pollutant levels during the city-lockdown periods were often reduced (He *et al.* 2020, Venter *et al.* 2020), although unexpectedly extreme levels were reported in some locations in China (Le *et al.* 2020), for likely diverse location-specific impacts on metabolic health.

Physical activity activates LINE-1 transposons

Related to viruses, are long interspersed element-1 (LINE-1) retrotransposons, genetic elements that re-insert and move about the human genome through a 'copy-paste' mechanism (Del Re & Giorgi 2020). These may be sensors of environmental stress with their activity regulated in different ways by environmental exposures (e.g. heavy metals, carcinogens, drugs, ionising radiation) and social interactions (e.g. maternal care, social isolation) (reviewed

by [Del Re & Giorgi 2020](#)). Interestingly, physical activity may promote LINE-1 transposon promoter activity in the hippocampus of the brain, as measured in L1-EGFP transgenic mice allowed access (or not) to running wheels ([Muotri *et al.* 2009](#)). The influence of physical activity-induced LINE-1 transposon activity on metabolic health has yet to be characterised.

Understudied interactions with physical activity

The impacts of changes in temperature – due to global warming and climate change – on physical activity and metabolic health are not well described, although increases in temperature and urbanisation (with shifts to motorised transport) likely reduce physical activity levels ([Swinburn *et al.* 2019](#)). [An *et al.* \(2018a\)](#) presented a conceptual model linking climate change with the obesity epidemic via urbanisation and other related societal shifts that likely promote physical inactivity. In addition, doing physical activity at higher temperatures may impact metabolic processes such as thermoregulation, via increased thermal strain particularly in at-risk populations (e.g. the elderly ([Waldock *et al.* 2018](#))). Personal sensors are available to measure an individual's personal exposure to temperature in the same context as physical activity and location for potential use in exposome studies ([Asimina *et al.* 2018](#)). Other understudied exposures include non-air pollutants such as mycotoxins, secondary fungal metabolites that contaminate food. These have been detected at levels in urine that sometimes exceed safety limits in participants ($n=94$) of the National Food, Nutrition and Physical Activity Survey (2015–16) living in Portugal ([Martins *et al.* 2019](#)). Similarly, widespread contamination of environmental biological and water specimens with pharmaceuticals, pesticides, illicit drugs and drugs of abuse, particularly cocaine, was recently detected across five sites in Suffolk, UK ([Miller *et al.* 2019](#)). These contaminants have been detected in many waterways and wastewaters throughout the world, with seepage into soils and ingestion by aquatic organisms ([Yadav *et al.* 2017](#)). How these events impact metabolic health is not well understood, although metabolic syndrome may occur frequently in people with addiction ([Singh Balhara *et al.* 2018](#)) and drug abuse ([Virmani *et al.* 2007](#)). This could be related to the capacity for some drugs (e.g. anti-psychotics) to interact with reward and energy balance pathways in the brain; however, these are complex drug-receptor interactions, which may be metabolically protective or harmful ([Siafis *et al.* 2018](#)). Importantly, school-based interventions that increase

physical activity levels may reduce substance abuse by teenagers ([Simonton *et al.* 2018](#)), with likely additional benefits for metabolic health. In further studies, reduced physical activity levels and increased blood levels of cadmium (a heavy metal) and the inflammatory acute-phase reactant, c-reactive protein, were associated with reduced telomere length (a sign of biological ageing) in a study of 461 environmental exposures in the NHANES cohort (1999–2002) ([Patel *et al.* 2017](#)). Findings from preclinical models suggest that exposure to endocrine-disrupting chemicals (e.g. bisphenol A) in early life (*in utero* and during lactation) may impair basal metabolic rate (respiratory quotient) and physical activity levels in female, but not male mice ([Johnson *et al.* 2015](#)). Increasing physical activity levels has been proposed as a means of overcoming the negative impacts of endocrine-disrupting chemicals; however, more research is needed to determine whether this is indeed the case ([Sargis *et al.* 2019](#)).

Further research is also needed to better understand how physical activity interacts with sociocultural determinants of metabolic health. It is likely that 'safer' neighbourhoods with reduced violence provide environments that support physical activity with positive associations between physical activity levels and neighbourhood safety and social cohesion, as observed in Mexican-Americans ($n=75$) living in Phoenix, Arizona ([Joseph & Vega-Lopez 2020](#)). Here, there are likely additional considerations of potential 'buffering effects' of more proximal influences on physical activity and other lifestyle risk factors for metabolic health, including genetics and social networks of individuals (family, friends). Furthermore, greater exposure to adverse child experiences (such as abuse, neglect, violence) was associated with a reduced likelihood of participants ($n=387$, Toronto, Canada) selecting physical activity as a behavioural change goal in adulthood ([Maunder *et al.* 2019](#)), with these individuals likely having less opportunity to establish healthy physical activity and other lifestyle-related behaviours early in life. Personal childhood trauma and exposure to traumatic events may contribute towards potentially addictive behaviours around food, alcohol and prescription drug use, including opioids sometimes prescribed for pain management for people with obesity ([Brady & Back 2012](#), [Sinha 2018](#), [Garami *et al.* 2019](#)). These addictive behaviours are also associated with increased risk for obesity ([Volkow *et al.* 2013](#), [Traversy & Chaput 2015](#), [Stokes *et al.* 2019](#)). A better understanding is needed around the impacts of the 'exposome of addiction' on physical activity and metabolic health including the combined impacts of physical, social

(e.g. interactions with others with addiction, or availability of support groups) and community (e.g. local attitudes towards addictive behaviours) environments (Stahler *et al.* 2013), as well as the impact of physical activity as a positive intervention for addictive behaviours. Finally, little research has been done around how societal values placed on the importance of physical activity and sports participation affect metabolic health, particularly in girls and women (Swinburn *et al.* 2019). As described below, new cohort-based studies are underway to discover the interactive effects of these, and many other environmental influences on metabolic and other health outcomes (Maitre *et al.* 2018, Jaddoe *et al.* 2020). Furthermore, future systematic reviews may uncover findings that more clearly delineate the role of sociocultural and other understudied elements of exposomes, and how they interact with physical activity to determine metabolic health.

Optimising environments for better physical activity outcomes

Indoor vs outdoor environments

Doing physical activity in indoors environments may sometimes be risky. Concentrations of some air pollutants can be higher in indoor settings, compared to outdoor locations where physical activity takes place (Andrade & Dominski 2018). These pollutants included carbon monoxide, CO₂, nitrogen dioxide (NO₂), fungi, and particulate matter and occurred in indoor locations such as ice-skating rinks, commercial and school gymnasiums and fitness centres (Andrade & Dominski 2018). Potential sources of these pollutants included ice-resurfacing machines (for NO₂ and particulates), and locations in which a high number of individuals undertake high-intensity activities indoors (for CO₂). Infection risk, particularly for viruses transmitted via contaminated surfaces or through the air, is likely enhanced in indoor exercise settings (Vardoulakis *et al.* 2020). Therefore, consideration of ways to limit exposure to indoor pollutants and infection risk through improved management and design of indoor exercise facilities is needed.

Of similar interest are findings of van Veldhoven *et al.* (2018), who identified substantial increases in exhaled breath levels of water disinfection by-products in adult volunteers following a 40-min swim in an indoor swimming pool. Levels of these by-products strongly correlated with the amount of physical activity (kcal, energy expenditure) undertaken by volunteers, and blood levels of metabolites of the tryptophan pathway (van

Veldhoven *et al.* 2018). However, it was not possible in that study to differentiate between the effects of physical activity and impacts of exposure to the disinfection by-products. Uncertainties also remain as to whether the same effects would occur in outdoor pool environments, and there may be possible further interactions through sun exposure and/or temperature that could modify the type and concentration of disinfectant by-products in water, as well as physiological responses. Interestingly, metabolites of the tryptophan pathway are endogenous ligands of the aryl hydrocarbon receptor and can be induced by exposure to UV light or synthesised by bacteria, with other known ligands of this receptor including pollutants such as polyphenols (Cella & Colonna 2015). Tryptophan metabolite-aryl hydrocarbon receptor interactions seem particularly sensitive to these (Cella & Colonna 2015, Vieyra-Garcia & Wolf 2018) and other environmental influences, including exercise and diet (e.g. vegetables (Kaiser *et al.* 2020)). It will be important to assess how exposures come together (in exposomes) to regulate this pathway, with likely impacts on metabolic health (Ghigliotti *et al.* 2014). These may be directly or indirectly influenced by the capacity of tryptophan metabolite-aryl hydrocarbon receptor interactions to regulate immunity (Cella & Colonna 2015, Rothhammer & Quintana 2019), inflammation (Vogel *et al.* 2020) and oxidative stress (Kaiser *et al.* 2020).

Better urban environments

Further consideration is needed in the design of urban environments to create beneficial exposomes for physical activity, particularly around increasing greenness and green spaces (Bos *et al.* 2014, Lu *et al.* 2015), and limiting air pollution. Unfortunately, poor air quality is often located in areas of high walkability (Hankey & Marshall 2017), as demonstrated in nationwide data from the Nurses' Health Study, in which positive correlations between walkability, population density and PM_{2.5} levels persisted after adjustments were made for differences in socioeconomic status (James *et al.* 2015). Similarly, commuting cycling networks are often developed alongside major traffic routes (Shrestha *et al.* 2020). Therefore, planning and construction of cycling infrastructure needs to be done in ways that limit personalised exposure to air pollution (Bos *et al.* 2014). In a system-dynamics modelling study of Auckland (New Zealand), the best policy scenarios for promoting cycling were tested, in which the impacts of injury, physical activity, fuel costs, air pollution and carbon emissions were assessed over 40 years. The policy

scenario that predicted the best health and environmental outcomes relative to cost, included provision of infrastructure that physically separated cyclists from urban roads, and instituted speed reductions (by traffic) on local streets (Macmillan *et al.* 2014). Other elements of the urban environment that could provide better exposomes for physical activity include those that may limit the impacts of air pollution (e.g. public transportation), and, improve walkability (e.g. pathways), safety (e.g. better street lighting) and greenness (e.g. vegetation and tree planting).

Future directions

International cohort studies and systematic reviews will help better define the influence of exposomes on health

The HELIX study (of 31,472 mother-child pairs) will have capacity to determine the influence of maternal and child physical activity on adiposity (e.g. BMI, skin-fold), cardiovascular (blood pressure) and other (lung health) outcomes across varying exposomes, characterising built environment (population density and public facility availability), and other urban (traffic, green space, noise), outdoor (ambient UV, air pollutants) and personal exposures (smoking, diet, pollutant and chemical) (Maitre *et al.* 2018). Similarly, the LIFECYCLE PROJECT-EU Child Cohort Network has recently been formed to examine the effects of exposomes on cardiometabolic (e.g. BMI, body composition, lipids, glucose, insulin) and other health outcomes, for which data will be harmonised from 19 birth cohorts of 250,000 children and parents to better understand the interacting effects of exposures including markers of socioeconomic status, lifestyle and nutrition, and urban environments (Jaddoe *et al.* 2020). Systematic review and meta-analyses of these new and previously published studies may help better understand how some less well-described elements of exposomes interact with physical activity and metabolic health. These will likely require careful formative work to identify keywords and scope beyond those used in this narrative review.

Natural experiments of the impact of built and natural environment-based exposomes on physical activity and metabolic health

Evaluating the impact of changes to urban design features or related policies (e.g. park revitalisation,

new transport infrastructure, congestion charging) on recreational and transport-related physical activity using a natural experimental design is a feasible and recommended alternative when randomised controlled trials are difficult and costly to undertake (Christian *et al.* 2013). Results from such natural experiments show that people living closer to places where there has been a built infrastructural change (e.g. a new cycle route) have higher cycling rates (Stappers *et al.* 2018), and urban policy that results in well-connected neighbourhoods with access to local parks of varying sizes increasing local recreational walking (Christian *et al.* 2017). Built and natural environmental interventions that target improving accessibility and connectivity, traffic and personal safety, and the experience of walking and cycling are likely to have the greatest impact on physical activity levels (Panter *et al.* 2019) and potentially metabolic health.

Measuring and controlling for genetic variability

Future studies will likely work towards integrating human genome and exposome data (via systems biology approaches) to better define specific gene-environment interactions and networks to evaluate the impact of personalised influences on metabolic health (Barouki *et al.* 2018, Jaddoe *et al.* 2020). Twin studies may also be a means of controlling for genetic variation. In a case study of a single pair of monozygotic twins with discordant physical habits, a twin with chronic endurance training for >30 years had increased myosin heavy chain (type 1) development, aerobic capacity (VO₂max), a better blood fat and sugar profile, and lower body fat levels, compared to their twin who did not train consistently during that time-frame (Bathgate *et al.* 2018). While further studies are needed to confirm these findings, examining twins with 'discordant physical habits' may be a novel means of better defining the effects of physical activity in varying exposomes. Another way to control genetic variability is through animal experimentation. Many exposures can be translated from real-world environments into the laboratory, including diet, physical activity (e.g. provision of running wheels), pollutants, smoking, alcohol intake, UV radiation, temperature, circadian rhythm and noise. Clearly, the influence of some human behaviours, social constructs and aspects of the built environment may be less easy to reproduce (e.g. socioeconomic status, poverty, crime, education), and while animal models are extremely helpful to define causality and identify mechanisms, they do not perfectly mimic human physiology and pathology.

New technologies and tools

New online tools are being developed that may help researchers better evaluate the interplay between the built environment, diet quality and physical activity on cardiometabolic outcomes. One example is 'KARMA', a web-based interactive tool, which allows participants to self-report destinations they visit, and anticipates travel routes based on the mode of transportation, which will be combined with accelerometry, food frequency questionnaires, and other data to provide a more complete understanding of participant's exposomes (Drewnowski *et al.* 2020). Similarly, the rapid uptake of smartphone devices with inbuilt capacity to measure physical activity (e.g. pedometer apps), and, global positioning systems (GPS) enable measurement of a person's physical activity and location in real-time and with geographical information systems (GIS) providing details on their physical environment (Stahler *et al.* 2013). As described earlier, other researchers have developed 'personalised monitoring kits' to characterise an individual's exposome (Donaire-Gonzalez *et al.* 2019). Initial findings suggest that ambient measures may correlate well with personalised measurements for some (e.g. personal and ambient levels of particulate matter absorbance), but not all (e.g. personal UV dose compared to ambient UV levels) exposures (Donaire-Gonzalez *et al.* 2019). However, it is important to recognise that measurement of exposures at a personal level is intrinsically difficult, costly, and maybe burdensome for participants, with potential compliance and privacy issues (e.g. GPS tracking, location-based technologies (Stahler *et al.* 2013)).

Conclusion

Exposomes have bidirectional effects on physical activity levels and metabolic health. Beneficial exposomes with green, natural outdoor spaces, physical activity resources and high walkability, promote physical activity and modest sun exposure, may combine with healthy diets to likely limit metabolic dysfunction. Conversely, physical activity may reduce the adverse impacts of high air pollution in some individuals, particularly when done in green spaces. There is more uncertainty around some features of exposomes such as viral infections, which may combine in unexpected ways with physical activity to modulate metabolic health. Future studies will likely provide a more nuanced understanding of the interactions between physical activity, exposomes and metabolic health, potentially with the development of more personalised

advice, such as better defining the optimal exposomes for physical activity, particularly for those at-risk of cardiovascular and metabolic dysfunction (Giorgini *et al.* 2016). Other important considerations will include how advice can be best tailored according to gender, ethnicity and age. However, many different levels of modifiable and non-modifiable factors affect physical activity behaviour, and our personal capacity to maintain or change our exposome may be limited. Similarly, exposomes are not static. A better understanding of how physical activity can be beneficial is needed (i.e. what type, intensity, frequency and duration), particularly to mitigate against the harms of more toxic exposomes, and in countries with high proportions of people living in poverty. Of particular significance is that exposome research brings together researchers and public health advocates that may not always have the same interests but do have the same goal (Swinburn *et al.* 2019) of driving synergies in improving the metabolic health of many people living in adverse exposomes around the world.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author contribution statement

S G conceived, designed and wrote the first draft of this review. A N L and H E C contributed significantly to content in the 'air pollution'/understudied interactions with physical activity' and 'introduction'/diet'/future directions' sections, respectively. Both provided editorial input throughout the drafting of the review.

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