

Sedentary Behavior and Chronic Disease: Mechanisms and Future Directions

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Background: Recent updates to physical activity guidelines highlight the importance of reducing sedentary time. However, at present, only general recommendations are possible (ie, “Sit less, move more”). There remains a need to investigate the strength, temporality, specificity, and dose–response nature of sedentary behavior associations with chronic disease, along with potential underlying mechanisms. **Methods:** Stemming from a recent research workshop organized by the Sedentary Behavior Council themed “Sedentary behaviour mechanisms—biological and behavioural pathways linking sitting to adverse health outcomes,” this paper (1) discusses existing challenges and scientific discussions within this advancing area of science, (2) highlights and discusses emerging areas of interest, and (3) points to potential future directions. **Results:** A brief knowledge update is provided, reflecting upon current and evolving thinking/discussions, and the rapid accumulation of new evidence linking sedentary behavior to chronic disease. Research “action points” are made at the end of each section—spanning from measurement systems and analytic methods, genetic epidemiology, causal mediation, and experimental studies to biological and behavioral determinants and mechanisms. **Conclusion:** A better understanding of *whether* and *how* sedentary behavior is causally related to chronic disease will allow for more meaningful conclusions in the future and assist in refining clinical and public health policies/recommendations.

Keywords: sitting, exercise, physical activity, physiology, epidemiology, cardiometabolic, mediation, measurement

Sedentary behaviors—seated or reclining postures done while awake and that require little energy expenditure (ie, ≤ 1.5 metabolic equivalents¹)—are ubiquitous in modern societies. Accelerometer-based estimates indicate that adults in high-income countries spend on average 8 to 10 hours per day sedentary.^{2–4} Prospective observational evidence suggests that high volumes of sedentary behavior are associated with an elevated risk for all-cause mortality, cardiovascular disease incidence and mortality, type 2 diabetes incidence, and some cancers, particularly among those who are not achieving recommended amounts of moderate- to vigorous-intensity physical activity

(MVPA).^{5–8} Moreover, observational studies^{9–11} and an accumulating body of acute experimental studies¹² suggest that specific patterns of sedentary time (ie, whether sedentary behavior is undertaken in more prolonged or shorter bout durations) may be differentially associated with several cardiometabolic risk biomarkers and premature mortality. However, this evidence base is still maturing.

As a result, the recently updated *2018 Physical Activity Guidelines for Americans* now recognizes the importance of reducing sedentary time.^{5,13} This new emphasis on shifting the balance away from high volumes of sedentary time in favor of *both* increased light-intensity physical activity and MVPA (notably of any bout duration) offers some important opportunities and targets from both a clinical and public health perspective. However, as limited evidence is available, concerning “optimal” amounts and patterns of sedentary behavior and light-intensity physical activity in relation to chronic disease risk, only general recommendations are possible to guide time spent in these behaviors at present (ie, “Sit less, move more”).

Accordingly, there is an impetus to investigate the strength, temporality, specificity, and dose–response nature of these associations to inform the development of more specific, time- and pattern-based clinical and public health guidelines for sedentary behavior. It will also be important to investigate whether observed associations are causal, and if they are, what the mechanisms linking sedentary behavior with chronic disease outcomes may be. To achieve this, *triangulation* of evidence using a range of different research approaches^{14–16}—each with different strengths, limitations, and sources of bias—will be required.

This paper stems from a recent research workshop (<http://www.mrc-epid.cam.ac.uk/ispahsedentary18/>) organized by the Sedentary Behavior Council themed “Sedentary behaviour mechanisms—biological and behavioural pathways linking sitting to adverse health outcomes” which was held in October 2018 just prior to the seventh

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International Society for Physical Activity and Health Conference (<https://ispah.org/congress-history/london-2018/>). The main aim of the workshop was to provide an up-to-date view on the state of the evidence on sedentary behavior mechanisms with respect to chronic disease, as well as to set an agenda for moving the science forward. This paper is not intended to be a full reflection of the workshop nor a systematic review of all research in this area. Rather, our objectives are to concisely (1) discuss existing challenges and scientific discussions within this rapidly advancing area of science, (2) highlight a few emerging areas of interest, and (3) point to pertinent future directions for sedentary behavior research.

Important Scientific Challenges and Debates

Are Sedentary Behavior and Physical Activity “Independent” Risk Factors?

The notion of *independence* tends to be interpreted in slightly different ways from a biological perspective (ie, distinct physiological effects/pathways); a behavioral intervention perspective (ie, unique correlates/determinants); and an epidemiological perspective (ie, covariate adjustment, effect modification/interactions, and/or examining time trade-offs between behaviors, etc). It is therefore unsurprising that how sedentary behavior is related to physical activity (or lack thereof), and whether sedentary behavior is an *independent* risk factor, remains an area of ongoing research and scientific discussion.^{17,18} Nevertheless, it could be argued that debates around the independence of sedentary and physical activity behaviors are somewhat artificial as these behaviors are inevitably *interdependent*—that is, it is not possible to alter sedentary time without also altering time spent in some form of physical activity (or sleep). Recent harmonized meta-syntheses indicate that the associations between self-reported sitting with all-cause and cardiovascular disease mortality are only partially independent of MVPA, but are particularly evident (or *modified*) in those who undertake insufficient (<150 min/wk) MVPA.^{7,8} Analytical paradigms such as compositional data analysis and isotemporal substitution—which can better account for behavioral interdependencies within a finite time or composition—are now being more widely implemented to address questions concerning the “ideal balances” of sleep, sedentary time, and different volumes and intensities of physical activity within observational studies.^{19–23} However, these approaches do not obviate underlying challenges concerning the accurate quantification of sleep, sitting/standing, and higher intensity activity behaviors across a 24-hour day with minimal burden (ie, using either single or multiple devices/inputs). Biological and behavioral intervention evidence is also needed to further build on the totality of evidence.

Does Sedentary Behavior Have Distinct Mechanistic Underpinnings?

As mentioned previously, initial animal model-based biological research (now a decade-old) and more recent human experimental studies examining muscle/adipose tissue samples have proposed that some sedentary behavior or muscle inactivity-related physiological effects may be *distinct* from those of associated with MVPA.^{24–29} However, this mechanistic evidence base remains sparse and is still maturing. Although some distinct mechanistic pathways linking sedentary behavior and MVPA to health may be plausible depending on the physiological outcome, experimental studies seldom rule out sedentary behavior as an “innocent bystander.” That is, whether the

effects of sedentary behavior are simply part of the broader physiological pathways associated with inactivity (sometimes colloquially referred to as “flip-sides of the same coin”).^{24,25} Importantly, the current consensus of understanding on the hypothesized mechanisms underlying sedentary behavior and chronic disease is largely based on expert opinion or narrative reviews, both of which are prone to bias. More targeted research is required to investigate the specific pathophysiological pathways through which sedentary behavior may independently influence chronic disease risk, and to what extent these pathways differ or overlap with those associated with insufficient MVPA and other health-related factors, such as age, sex, nutrition, sleep, cardiorespiratory fitness, or adiposity.

How to Quantify and Manipulate Specific Behaviors for Health Promotion?

Individuals and populations can engage in a wide variety of behaviors and activities on an hourly and daily basis. Thus, it is challenging to clearly separate out the distinct behavioral determinants and biological effects of short or prolonged sitting accumulation patterns versus other behaviors; such as seated fidgeting, active or passive standing, or more dynamic light- or moderate- to vigorous-intensity activities of various modalities. For example, debates as to whether postural changes alone (ie, passive standing) are a “healthier” alternative to sitting remain somewhat unclear, due in part to historically unclear definitions, inadequate measurement capacities or confounding factors. Although systematic and direct manipulation of specific behaviors in tightly controlled acute “proof-of-concept” human experimental trials (usually hours in duration) with intermediate cardiometabolic risk outcomes is possible, gathering longer-term randomized controlled trial evidence (weeks to months) is a major undertaking with significant cost implications and thus requires adequate justification.

In many instances, it tends to be much easier to generate hypotheses based on observational research than it is to operationalize robust/generalizable experimental tests to simulate these variations in the context of our behaviorally complex daily lives.^{30,31} However, as is the case with most behavior-related observational research, measurement error, residual confounding, and reverse-causation are important limitations and challenges in the sedentary behavior field. Thus, while high-quality longer duration randomized controlled trial evidence remains a key priority, it is not without limitations and the previously mentioned factors reemphasize that no single approach will be sufficient to improve our understanding of the mechanisms that may link sedentary behavior with chronic disease. These challenges underscore the need for a variety of different research methods and perspectives, carefully tailored and systematically implemented study designs, along with advanced measurement and analytical approaches; simply put, triangulation of evidence.

Recent Areas of Interest and Future Directions

Measurement Systems and Data Labeling Methods

Accurate measurement remains fundamental for documenting overall levels and accumulation patterns of sedentary time, understanding determinants and dose–response relationships with specific health parameters, and evaluating the efficacy and effectiveness of sedentary-reduction interventions. New questionnaire methods with reasonably valid estimates and contextually rich data (eg, activities

completed over time in 24 h^{32,33}); emergent device-based technologies^{34–36}; and analytic methods show considerable promise in sedentary behavior assessment. In addition, trends toward device miniaturization and longer battery life, and interoperability of existing devices/logs (eg, accelerometers, electromyography, smartphones, global positioning systems, ecological momentary assessment, or domain-specific logs), are making the collection of continuous, time-stamped data more accurate and feasible and will no doubt provide unique insights and opportunities in the future. However, challenges remain with reproducibility, attaining compliance with measurement protocols (particularly in large samples), and the development and application of complex analytical methods with high levels of generalizability. Thigh-worn accelerometers (eg, ActivPAL™; PAL Technologies, Glasgow, Scotland) are currently the criterion standard for distinguishing sitting from nonsitting postures in field-based studies and are proving valuable in intervention studies to help understand potential unique contributions of different postures and activity types with health outcomes. Population-level studies incorporating thigh-worn accelerometers are, however, much smaller than those which use wrist-worn devices (eg, the UK Biobank Study³⁷), in large part due to differences in convenience and cost.³⁸ In this regard, new collaborative research platforms such as the Prospective Physical Activity, Sitting, and Sleep consortium—which aims to pool together existing and future observational studies of thigh-worn accelerometry—show potential and are currently being developed.³⁹

As wrist- and hip-worn accelerometers are more commonly used in population-level research investigating the activity spectrum, a priority of future research will be to develop new computational methods for processing data to derive valid estimates of posture-based sedentary patterns under free-living conditions. Newer statistical and computational methods aimed at better characterizing sedentary and physically active behaviors from single devices are being developed and tested.^{40–42} Alternatives to threshold-based methods of classifying accelerometer “counts” have started to emerge, including those that incorporate machine learning models. For example, in the largest study of its kind to date, Willetts et al⁴³ used wrist-worn accelerometer data from UK Biobank and applied machine learning methods to identify when participants were sitting, standing, sleeping, bicycling, walking, or exercising. Models were trained in a free-living subsample, rather than constrained laboratory environments, and evaluated against reference wearable cameras,^{44,45} time-use, and sleep diary information sources (mean accuracy of 87% with a kappa interrater agreement score of .81 over all the behavior types). The ability to infer sitting behaviors at the population scale, along with a variety of other fine-grained activity behaviors such as standing and other activity types, holds great promise for better informing causal inferences about potential health consequences and mechanistic pathways (eg, see “Genetic Epidemiology” section). These algorithms could also be potentially used to classify patient data from clinical trials, but efforts are still required to enhance wider accessibility, scalability at low cost, and greater ease of use for all nonprogrammers/engineers.

Future Directions.

- (1) Can subjective and time-stamped data from devices be integrated to more accurately characterize posture, muscle activity, and physical activity types/patterns under different contexts?
- (2) Can the field progress toward the use of accessible, reproducible, large-scale measurement protocols across the entire spectrum of human movement behaviors, to aid prospective harmonization and future consortium-based work?

Genetic Epidemiology

The identification of genetic and epigenetic factors related to robustly tagged physical activity and sedentary behavior phenotypes is an emerging research focus^{46,47} that may help provide improved causal insights into the complex biological pathways linking both physical activity and sedentary behavior with chronic disease. Findings therefore have the potential to strengthen clinical/public health messages around more specified behaviors and/or inform the development of mechanism-tailored prevention strategies.

Building upon their accelerometer-based behavioral phenotypes validated in free-living environments (using machine learning methods), Doherty et al⁴⁷ recently reported results from a large genome-wide association study of UK Biobank suggesting that the amount of time spent sedentary (heritability estimate: $h^2 = 15\%$), sleeping ($h^2 = 19\%$), or moving ($h^2 = 21\%$) may be partly genetically determined. How sedentary behavior influences epigenetic expression is also just starting to be explored. For example, van Roekel et al⁴⁶ recently examined cross-sectional associations of self-reported TV viewing and sitting time with DNA methylation measured in peripheral blood. They found weak evidence ($P < 1.0 \times 10^{-5}$) for 14 non-overlapping 5′—C—phosphate—G—3′ sites. However, for most (11 of the 14) 5′—C—phosphate—G—3′ sites, higher volumes of sedentary behavior were associated with higher methylation levels. This work is of interest as locus-specific blood DNA methylation is hypothesized to be a mediating factor in the contribution of lifestyle components to the development of chronic disease.⁴⁸

Doherty et al⁴⁷ also used *Mendelian randomization*—where genetic variants serve as instrumental variables to estimate whether the risk factor correlated with the genetic variant is causally related to the outcome of interest (eg, Figure 1)⁴⁹—to provide evidence that overall physical activity may causally lower diastolic blood pressure and the odds of hypertension. However, no statistically significant associations were observed for sedentary behavior with any health outcomes. Discovery set sample sizes are, however, currently a limiting factor in these analyses, as genome-wide significant loci currently only explain 0.08% of variation in sedentary behavior. It should be noted that examining causal relationships of physical activity and sedentary behaviors (and their subcomponents) using Mendelian randomization is subject to some limitations at present, including weak instruments (ie, instrumental variables explaining

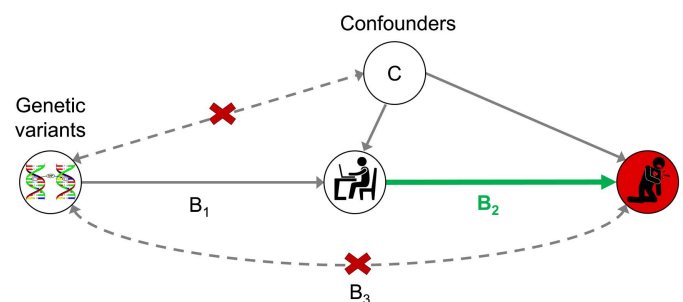


Figure 1 — Mendelian randomization models aim to provide a natural experiment (causal estimate), similar to a randomized trial, in observational data, using genetic variants as instrumental variables. Because alleles are allocated randomly at conception, they are theoretically independent of environmental and other confounding factors. Solid pathway lines are theorized to exist; dashed pathway lines are theorized to be nonsignificant according to model assumptions. B_2 indicates the estimated causal relationship ($B_2 = B_1/B_3$). B_1 and B_3 indicate the estimated direct effects of a genetic variant on the exposure (eg, sedentary behavior) and outcome (eg, chronic disease).

a relatively small proportion of variance in sedentary behavior, leading to loss of statistical power and other biases), and the possibility of pleiotropy (ie, genetic variants influencing the outcome via a different biological pathway from sedentary behavior, leading to inaccurate causal estimates and loss of statistical power). Improvements in measurement and behavioral characterization (see “Measurement Systems and Data Labeling Methods” section) may help to reduce some of these issues in the future and help provide further insights. Replication of genome-wide association study findings in more diverse data sets will also be important to progress this field, including further research on how underlying genetic and epigenetic features related to sedentary behavior may influence chronic disease development.

Future Directions.

- (1) Can better measurement and data labeling methods help to more strongly distinguish between the genetics of sedentary behavior and physical activity (current genetic correlation = .59)?
- (2) Can better genetic instrument variables be identified to support Mendelian randomization studies of sedentary behavior with disease outcomes?
- (3) Can current genetic and epigenetic discoveries related to sedentary behavior be replicated in other (ie, non-European) populations?

Causal Mediation and Other Analytic Methods

Observational studies can contribute to a better understanding of the role and relative importance of potential biological pathways linking sedentary behavior to chronic disease by measuring relevant intermediate agents on these pathways and performing formal mediation analysis.⁵⁰ Such methods allow for partitioning of an overall association between sedentary behavior and chronic disease into *indirect* effects (ie, the association through the mediator[s] of interest) and *direct* effects (ie, the association not through the mediator)—see Figure 2. This information will not only help to advance our scientific understanding of potential causal pathways

and underlying mechanisms but could also help to identify potential targets for intervention—particularly given the challenges of conducting long-term randomized controlled trials. Traditional methods for mediation analysis (ie, the difference and the product methods) that have been available for more than 30 years can be used successfully to assess mediation in simple settings with one mediator of interest, where there is no exposure–mediator interaction, the outcome is continuous or binary and rare, and a number of no confounding assumptions are met.⁵⁰ However, recent advancements in methodology and the development of a more sophisticated approach to mediation analysis—broadly referred to as causal mediation analysis—has made it more feasible to investigate more complex settings. These new methods are rooted in the counterfactual view of causation and allow partitioning of the overall association for any type of outcome under the same no confounding assumptions required by the traditional methods, and in the presence of exposure–mediator interaction.⁵⁰ It is important to note that causal mediation analysis methods, similar to other statistical methods, make important assumptions about the causal structure of the associations between variables (ie, temporality). For example, determining whether adiposity or physical function confounds or mediates the association (ie, is in the causal pathway) of sedentary behavior and chronic disease when measured cross-sectionally is challenging and generally requires strong *a priori* assumptions (Figure 3A).

Future Directions.

- (1) Can contemporary mediation analysis approaches provide new and important insights on potential mechanistic pathways linking sedentary behavior with chronic disease outcomes?
- (2) Can more advanced causal mediation analysis methods improve inferences about the causal structure of associations between sedentary behavior and chronic disease outcomes (Figure 3B) while accounting for multiple mediators that influence or interact with each other^{51–54} over repeated measurements.
- (3) Can the integration of causal mediation with additional approaches such as compositional or isotemporal paradigms^{19–22} provide useful information when considering interdependencies

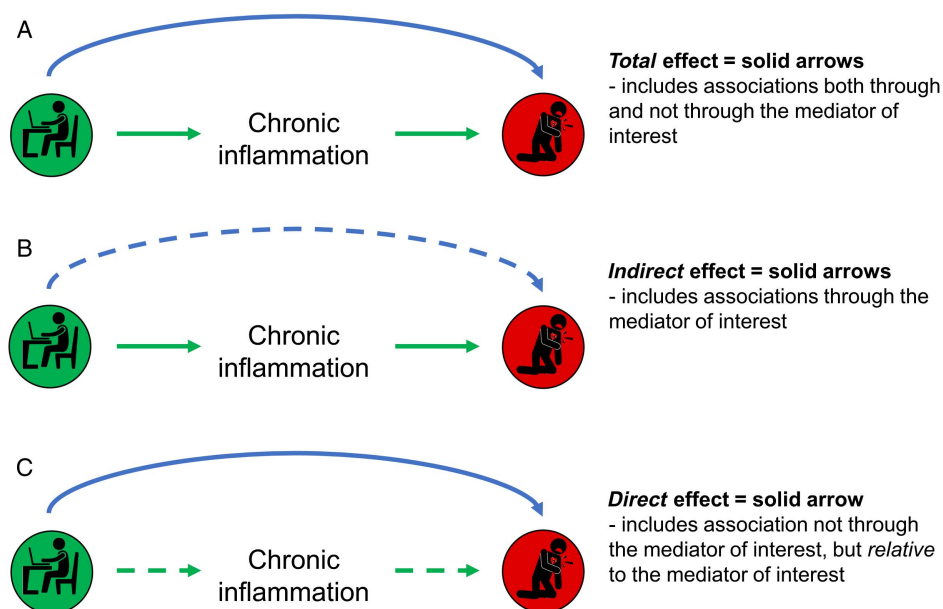


Figure 2 — Mediation of the association between sedentary behavior and chronic disease, using chronic inflammation as a theoretical example. Panels A, B, and C illustrate the partitioning of total, indirect, and direct effects.

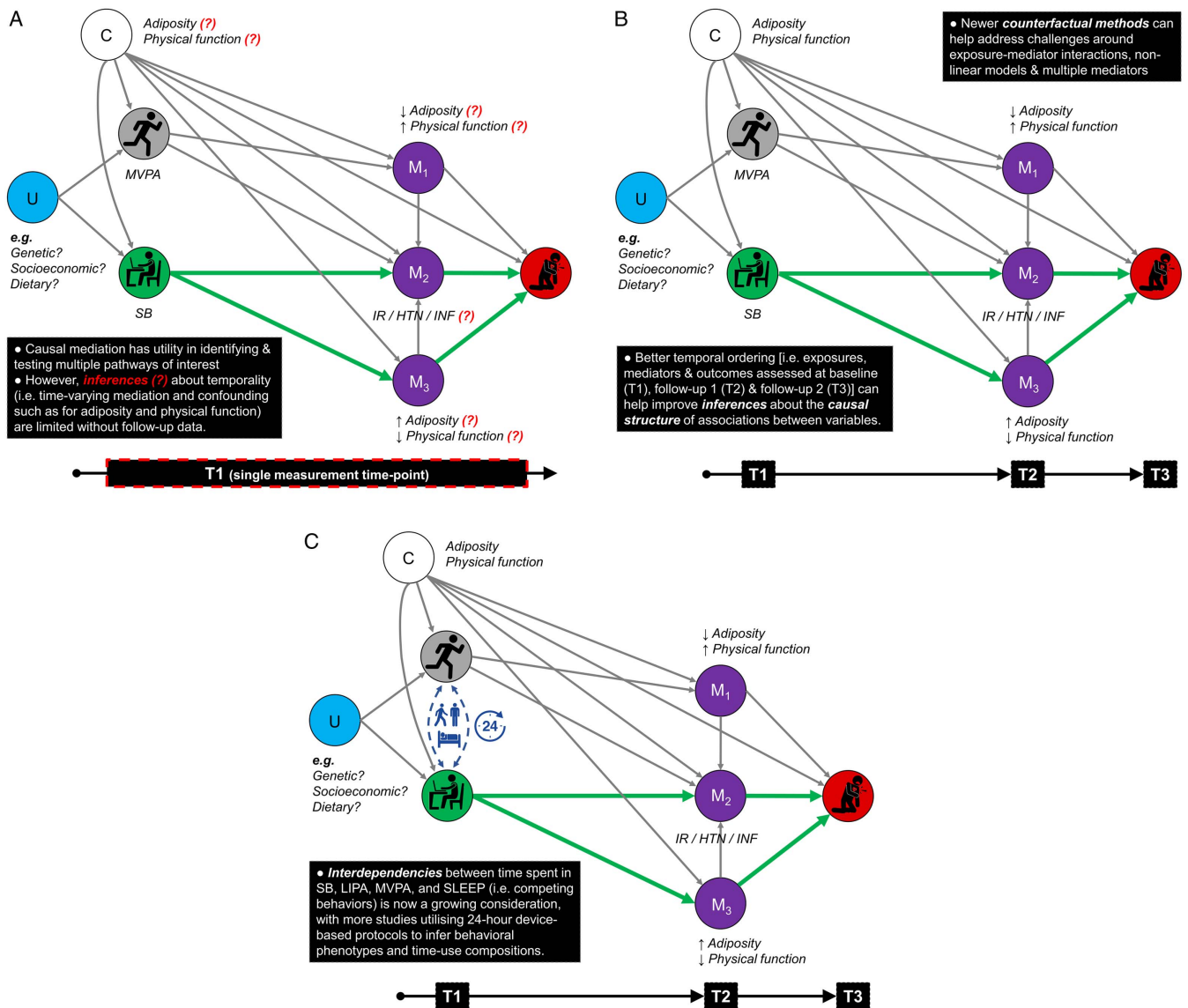


Figure 3 — DAG of the association between SB and chronic disease, through potentially similar and distinct pathways to MVPA. Variables are labeled as exposure (green in online; SB), outcome (red in online; chronic disease), mediators (purple in online; M), confounders (white in online; C), or unmeasured confounders (blue in online; U). Theoretical examples of adiposity and physical function are used—which may plausibly be confounders or mediators—alongside other potential risk factors in the pathway, such as IR, HTN, and chronic INF. Assumptions and challenges are noted in the black boxes. Causal mediation analyses would ideally be applied using data from multiple waves of follow-up to improve causal inferences (ie, panels A to B; time-points T1→T3). It may also be relevant to consider and integrate inevitable interdependencies, effect modification, and/or interactions between multiple behaviors, as part of the broader causal structure of associations (panel C). DAG indicates directed acyclic graphs; HTN, hypertension; INF, inflammation; IR, insulin resistance; LIPA, light-intensity physical activity (including standing); MVPA, moderate-to-vigorous-intensity physical activity; SB, sedentary behavior.

between sedentary behavior and other competing behaviors (ie, physical activity and sleep) that make up the 24-hour day (Figure 3C)?

Experimental Studies

Experimental evidence from controlled laboratory trials and free-living intervention studies is crucial in providing a better understanding of biological plausibility, the causal structure of relationships, and potential mechanistic pathways linking sedentary behavior with adverse health outcomes. Building on the findings of observational studies, well-controlled human experimental studies are beginning to examine the physiological impact of prolonged

uninterrupted sitting time relative to sitting interrupted by various countermeasures (eg, standing, light- to moderate-intensity walking, upper and lower body cycling/pedaling, and even body-weight resistance activities). Studies like these can provide useful physiological insights as well as help illuminate pragmatic “proof-of-concept” questions and hypotheses such as: “Is just standing enough, or do I need to move/ambulate more?” “Do I need to stand if I have a pedal desk?” “How long can I sit for?” “What mode of ‘activity break’ should I do and at what intensity?” or “If I cycle or run on my commute, can I afford to sit more at work?”

The findings of these recent studies have already been reviewed elsewhere in greater detail^{12,24,25,55–57}—with emerging areas of interest and potential mechanisms underlying various

chronic disease outcomes also reviewed in those particular contexts. As a brief summary, hypothesized mechanisms (notably, still based largely on inactivity physiology paradigms, see Figure 4) include systemic/habitual reductions in both muscular/metabolic demand and blood flow/shear stress, muscle atrophy, postmeal nutrient loading, decreased lipid trafficking/oxidation, and concurrent decrements in muscle/liver insulin sensitivity and vascular function—all of which, in turn, would likely promote whole-body insulin resistance, intraorgan lipotoxicity (or ectopic fat storage), decreased mitochondrial oxidative capacity, oxidative stress, low-grade inflammatory cascades, and interorgan metabolic signaling. Peripheral^{58–62} and cerebrovascular hemodynamics^{63,64} and perturbations in sympathetic regulation⁶⁵ may also be implicated, but these are harder to measure well in human intervention studies, and thus the evidence base remains scant. Nevertheless, when sedentary behavior is habitual, it is likely that the above factors contribute to the development of clinical risk factors—such as hyperglycemia, dyslipidemia, and hypertension—promoting vascular damage and progression toward serious metabolic and cardiovascular complications, and the exacerbation of other chronic diseases. Much more research is still needed, however, to elucidate both direct and indirect pathophysiological consequences over the short and long term as well as the potential mechanisms involved.

Future Directions.

- (1) Are the specific *physiological effects* of sedentary (sitting) behaviors, if apparent, mediated predominantly by local/systemic skeletal muscle inactivity or by seated postures per se, and what is the likely importance of these mechanisms for disease-specific pathologies (eg, dysmetabolism, vascular

dysfunction, cognition, central and peripheral neural effects, etc)?

- (2) What activity interventions or postural perturbations from sedentary behavior (eg, frequency, length, and type/mode of activity) are required to favorably alter physiology over the short (eg, 1–7 d) and longer term (weeks to months) in both controlled and real-life settings, in *whom* (eg, women, obese, unfit, etc), and under what *contexts/settings* (eg, relative to meal timing, while in energy deficit/surplus, in the workplace, under stress, while sleep deprived)?
- (3) What other nontraditional cardiometabolic risk markers, cellular or molecular mechanisms, and organ-specific pathways are affected by acute and habitual sedentary behavior patterns, and how do these local (eg, muscle, adipose tissue) and systemic (eg, metabolic, inflammatory) physiological effects integrate to elicit pathophysiological consequences?

Behavioral and Biological Determinants/Mechanisms

Although the focus of this paper has primarily been on biological pathways linking sedentary behavior and chronic disease, there remain many important behavioral determinants to better understand and elucidate. Significant knowledge gaps and ambiguity still exist concerning the individual, social, and environmental factors that influence sedentary behavior.^{66,67} Most studies to date have examined correlates rather than determinants—limiting inferences about causality and underlying behavioral mechanisms. A more thorough and systematic approach to studying the determinants and behavioral mechanisms that influence sedentary behavior (ie, as a dependent variable rather than an independent variable or mediator of change) is needed to design more specific, targeted, and effective interventions. However, this important phase is sometimes bypassed and progressed to designing interventions when there is insufficient evidence to help identify the factors that may be most beneficial to target.^{68,69}

It has been argued that the ubiquitous, habitual, and socially/environmentally reinforced nature of sedentary behaviors may point to unique determinants that are distinct from traditional strategies used to increase MVPA participation.^{66,70–72} While individual-level theories for MVPA tend to focus on the role of conscious decision-making or *reflective* processes (which are usually finite⁷³), approaches targeting sedentary behavior may need to allow for more emphasis on unconscious decision-making or *automatic/impulsive* processes (ie, cues/nudges/habits)—which tend to govern a substantial share of our behavior.^{74–76} Moreover, research examining *where* and *why* people are sedentary (and its temporal dimensions within and between individuals) may help to identify both *macroenvironmental* and *microenvironmental* factors and contextual cues to target (eg, combinations of environment/location, physical objects, time of day, emotional state)—some of which may be more amenable to behavioral and policy changes than others. Consideration of these factors will be crucial in informing the design and implementation of effective, evidence-based interventions to reduce sedentary time.

It may be justifiable that sociocultural, motivational, and environmental factors tend to receive the greatest focus when seeking to intervene on sedentary behavior. However, as mentioned previously (see “Genetic Epidemiology” section), there remains a paucity of evidence on which intrinsic biological factors are important determinants or regulators of sedentary behavior (and physical activity). Indeed, a growing body of research in both humans and animals suggests that intrinsic biological factors also

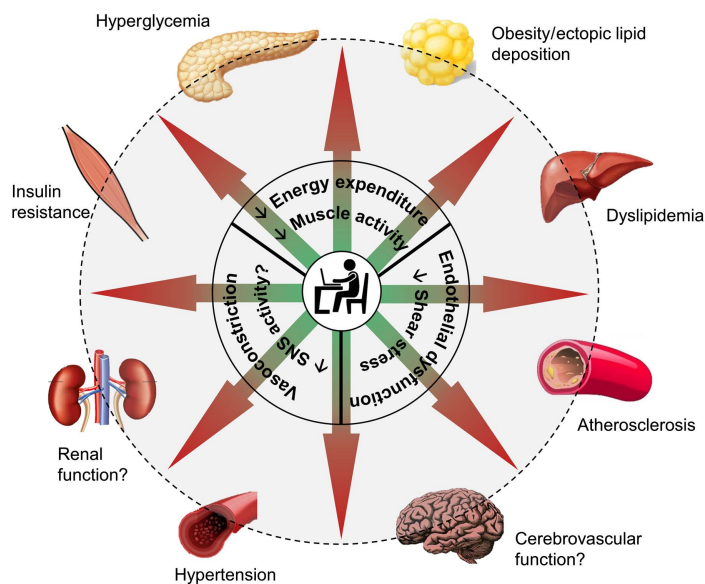


Figure 4 — Hypothesized mechanisms linking sedentary behavior with chronic disease risk factors. Underlying biological responses to sedentary behavior/inactivity that may drive disease pathophysiology are likely to be multifactorial, involving peripheral organs that are known to play a key role in metabolism (ie, skeletal muscle, liver, and adipose tissue), SNS activity and peripheral/cerebrovascular hemodynamics, and oxidative stress and inflammatory signaling pathways. Dose–response relationships are likely to vary according to specific mechanisms and organ-specific pathways, and their interaction over the short and longer term. SNS indicates sympathetic nervous system.

play a key role in the regulation of daily physical activity.^{77–83} These may include influences on brain circuitry related to personality, affect regulation, relative reinforcing, and reward processing, or via influencing cardiorespiratory and muscle capacity/function to regularly engage in physical activity. These elements are likely to also interact with self-efficacy and other core components of social-behavioral models for both physical activity and sedentary behaviors⁸⁴; thus, is it important that they are better integrated to improve our understanding of the overall scientific picture. Additional biological factors and pathways that could be worthwhile to explore further in the context of sedentary and physical activity behaviors (and our ability to intervene or identify therapeutic strategies) could include epigenetic events, early life experiences, and biological intermediates such as dietary, stress, and toxicant/pollution exposures.

Future Directions.

- (1) Can important behavioral and biological determinants or regulators of sedentary behavior be identified more rigorously and better understood within different contexts?
- (2) Can the efficacy and effectiveness of behavioral interventions, guided by underlying biological and behavioral determinants and theories and behavior-change techniques, be improved through a better understanding of *when*, *where*, and *why* different people engage in sedentary behaviors?

Conclusion

In this paper, we have described several major unanswered research questions concerning the observed associations of sedentary behavior with adverse health outcomes. The etiological and mechanistic factors underlying such associations are multiple, complex, and challenging to study. However, a deeper causal and mechanistic understanding remains an important scientific endeavor to help advance the field and improve chronic disease prevention and management. There is a need to acknowledge these inherent complexities and carefully seek to better understand them through the application of rigorous interdisciplinary science. Triangulation of evidence from observational, biological, behavioral, and experimental research will be essential. Moreover, improvements and refinements in measurement methods, research-designs, and statistical analysis techniques will also contribute greatly to our understanding of *whether*, *how*, and *why* sedentary behavior is causally related to chronic disease. Advances in these areas will allow for more meaningful conclusions on the relationship between sedentary behavior and chronic disease and assist in refining both clinical and public health policies and recommendations in the future.

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