Sitting and chronic disease: where do we go from here?

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A significant contribution to this issue of Diabetologia is the observational study by van der Berg et al. (1). They examined the cross-sectional associations of objectively measured sitting with type 2 diabetes and cardio-metabolic risk in a sample of nearly 2,500 middle-aged Dutch adults, enriched for type 2 diabetes patients. This study is an important addition to the literature aiming to examine health consequences of sedentary behaviour, recently defined as any waking activity with low energy expenditure and performed in a sitting or reclining posture (2). The most important asset of the work by van der Berg et al. (1) involves the implementation, in a large participant sample, of a thigh-worn activity monitor that accurately discriminates between sitting/lying and non-sitting/lying postures. Using this methodology they were able to relate total sitting time and indicators of sitting patterns (i.e. the manner in which sitting time is accumulated) with glucose metabolism status and prevalence of metabolic syndrome criteria. They found that each additional daily hour of sitting time was significantly associated with increased odds of having type 2 diabetes (1.22 (95%CI, 1.13, 1.32)) and the metabolic syndrome (1.39 (95%CI, 1.27, 1.53)). This finding was irrespective of time spent in higher-intensity activity and a wide range of socio-demographic, behavioural and health-related confounding factors. The accumulation patterns of this sitting time, whether examined as number of interruptions in sitting, number of prolonged (i.e. ≥30 minutes) sitting bouts or average sitting bout duration, however, showed much weaker associations.

**Clinical and public health relevance of sedentary behaviour**

The interest in sitting as a risk factor for type 2 diabetes was initiated 15 years ago by Hu et al. (3;4). They were the first to associate high levels of TV viewing and other types of sedentary behaviour with increased risk for incident type 2 diabetes. As highlighted in a fairly recent meta-analysis in this journal (5), the link between sedentary behaviour and type 2
diabetes is one of the most consistently observed in this field – a field which has experienced an exponential rise in scientific, media, and general community interest. This increased interest has also resulted in the emergence of preliminary public health guidelines focusing on reductions in prolonged sitting (e.g. (6)).

The sedentary behaviour research area is, however, still fairly young; both in terms of advancements in measurement methodology as well as establishment of robust observational longitudinal and experimental evidence. Current meta-analytical effect estimates are predominantly based on self-reported estimates of sitting time, which are associated with substantial measurement error. Studies with accurate measurement of sitting posture, such as the one by van der Berg et al. (1), are therefore most welcome, especially if they will also extend to a longitudinal design, to minimise the risk of reverse causality (i.e. when individuals, already on the disease pathway, therefore display or report more sitting). To explore whether reverse causality affected results in their cross-sectional study, the authors ran a sensitivity analysis in which they excluded participants with type 2 diabetes on insulin medication (who were assumed to be more severe patients). This did not change overall results. However, a major limitation of cross-sectional research is the lack of inference on temporal sequence between exposure (e.g. sedentary time) and outcome (e.g. type 2 diabetes), which inherently will always be associated with substantial risk of reverse causality. Another common limitation in this research area is residual confounding for poorly or unmeasured confounders. This is when a relationship is estimated incorrectly because a confounding factor was not measured (such as dietary intake, as acknowledged by the authors) or not sufficiently accounted for (such as moderate-to-vigorous physical activity, as described further below).
These difficulties hamper our current understanding of the exact impact prolonged sitting may have on the development of chronic disease, such as type 2 diabetes. Excessive sedentary time is however ubiquitous in most modern societies, both at an inter- (i.e. in the majority of individuals across all age groups) and intra-individual level (i.e. on average more than half of the waking day) (7). This means that even if true effect estimates would be relatively small, the potential population impact of any behaviour change in terms of prevention of type 2 diabetes and other chronic disease may still be relevant.

Opportunities to improve the evidence base

1. Patterns of sedentary time: optimising its operationalization in observational research

Unlike other health behaviours, for example smoking, where even minimal exposure such as passive smoking may increase risk, not all sitting is harmful. Indeed, some sitting is needed for rest and recovery, and prolonged time spent in non-sedentary postures (e.g. static standing) also has inherent risks. Attention has therefore now shifted to also considering, and intervening on the patterns of sedentary time, i.e. how sedentary time is accrued.

Definitions of sedentary patterns in the study by van der Berg et al. (1) and previous observational studies are variable. This testifies the relatively recent interest in this behavioural construct as a potential independent health hazard. Healy et al. (8) introduced this concept by relating the number of “breaks” or interruptions in sedentary time to specific cardio-metabolic risk factors. This breaks construct, which has been incorporated into public health messages, is now widely used in studies looking into accumulation patterns of sedentary time. However, this frequency measure may not be the most robust estimate of patterns of sitting time, partially because it does not directly assess duration of prolonged...
sitting bouts per se (9). Other indicators have therefore also been considered, some also frequency-based (e.g. number of prolonged bouts), others more duration-based (e.g. average sedentary bout duration). As also shown by van der Berg et al. (1), these different constructs show different strengths of associations, which indicates that they may not relate equally strong to the same latent construct of “prolonged sitting”. This diversity may complicate comparisons between study results and general inference about the health importance of sitting patterns. More work is therefore needed in terms of optimising and harmonising pattern definitions for observational research. Constructs which are conceptually more proximal to assessing prolonged sitting per se may need to be used more universally, such as time spent in bouts of minimal durations (e.g. ≥30 minutes). These constructs also easily translate in terms of public health guidelines (e.g. “Get up at least every 30 minutes.”), if they were to be associated with increased health hazard. Concurrently, more studies should implement posture-discriminating methods that can accurately distinguish sitting from standing, and therefore also identify the transitions between these postures.

2. Integrating the use of improved measures of sitting time, higher-intensity activities, and domain-specific information

As mentioned above, the study by van der Berg et al. (1) should be commended for the use of posture-discriminating accelerometry. This is currently rare on such a scale, compared to the vast majority of existing literature which has implemented traditional hip- or waist-mounted accelerometers (10). Despite this, however, time spent in moderate-to-vigorous physical activity, an important co-variate, was measured in a more rudimentary manner. This problem, common in this field of research, could be overcome in future research by combining different objective inference methods, each specialised in accurately capturing specific subcomponents of the intensity or posture-based spectrum of activities. Further important
opportunities involve the integrated use of simultaneously measured domain-specific information (e.g., through domain-specific logs or GPS), ensuring participant burden remains low. This would allow understanding of the context of the behaviour and associated opportunities for intervention.

3. Considering the 24-hour clock

Notably, activities do not occur in isolation— but rather are interdependent. That is, given a 24-hour day, time spent in one activity necessarily displaces time spent in another. The impact of sedentary time is therefore not only due to the time spent in a low energy, low muscle contractile state, but also due to the loss of time spent in higher-intensity activities. An individual’s health is impacted by the relative balance between sleep, sedentary behaviour and physical activity. More advanced analytical techniques, such as iso-temporal substitution modelling and compositional data analysis, have recently been introduced in sedentary behaviour/physical activity epidemiology. These approaches aim to account for this interdependency of activity behaviours in aetiological analyses with health outcomes. They therefore provide more realistic insights in the relative impact of behaviour change from one part of the intensity spectrum to another, using observational data. As expected, these models have typically shown that shifting time from sedentary to moderate- or vigorous-intensity activities generally has the greatest benefit on markers of cardio-metabolic health (13). However, given the challenges associated with increasing population levels of moderate-to-vigorous-intensity activity, it is encouraging to note that some cardio-metabolic benefits may be achieved with shifts from sedentary to light-intensity activities, including standing (14). An important consideration in the use of these techniques is the assurance that they provide us with insights which are informative and easily translatable into public health guidance.

4. Establishing robust evidence in a prospective and global setting
The van der Berg et al. study (1), and the vast majority of other observational studies which related objectively measured sedentary time with health outcomes, have been cross-sectional. This is because implementation of these activity monitors in larger aetiological studies is a more recent development, especially those monitors which are able to accurately discriminate between postures (10). Future longitudinal assessment in cohorts such as the Maastricht study (1) will reduce the potential risk of findings being affected by reverse causality. As effect estimates for some of these associations may also be fairly small, future data sharing between multiple cohorts will facilitate an increase in statistical power. This provides additional opportunities in terms of understanding differences in dose-response associations within and between populations. Given the predominance of non-posture-discriminating methodologies in ongoing cohorts, this may also encourage endeavours to harmonise data between different methodologies (10).

In terms of experimental research, several lab-based physiological trials have indicated the potential acute benefits of breaking up prolonged sitting, especially in terms of limiting post-prandial glucose and insulin excursions (e.g. (15)). Future acute physiological trials, with further control for the frequency, duration and intensity of breaks, will advance our understanding of the physiological underpinnings of observational findings. Alongside these lab-based studies, on-going free-living intervention research is providing evidence of the feasibility of changing prolonged sitting behaviour (16). These studies now need to be followed by trials which are sufficiently powered to allow assessment of the longer-term effects of changes in free-living sitting on cardio-metabolic and other health outcomes. These trials should also control for compensatory effects in terms of sitting behaviour and total energy expenditure.

**Conclusion**
We applaud the study by van der Berg et al. (1), which provides important new insights in this area of research. Robust findings from future longitudinal observational and experimental studies, which engage with the wealth of current and future opportunities, are now needed. These will place us in a better position 1) to make more realistic inferences about the public health impact of changing activity intensity levels in a balanced, efficient and realistic manner, 2) to subsequently advocate more refined public health guidance in line with this evidence and, last but not least, 3) to translate these insights into individual, micro- and macro-level societal changes, which reduce the public health burden associated with the distorted balance in activity intensity levels, as currently witnessed around the world.

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**Duality of interest**

The authors declare that there is no duality of interest associated with this manuscript.

**Contributions**

Both authors were responsible for drafting the article and revising it critically for important intellectual content. Both authors approved the version to be published.
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