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Cardio-metabolic impact of changing sitting, standing, and stepping in the workplace

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ABSTRACT

Background: According to cross-sectional and acute experimental evidence, reducing sitting time should improve cardio-metabolic health risk biomarkers. Furthermore, the improvements obtained may depend on whether sitting is replaced with standing or ambulatory activities. Based on data from the *Stand Up Victoria* multi-component workplace intervention, we examined this issue using compositional data analysis — a method that can examine and compare all activity changes simultaneously.

Methods: Participants receiving the intervention (n=136 \geq 0.6 full-time equivalent desk-based workers, 65% women, mean \pm SD age=44.6 \pm 9.1 years from seven worksites) were asked to improve whole-of-day activity by standing up, sitting less and moving more. Their changes in the composition of daily waking hours (activPAL-assessed sitting, standing, stepping) were quantified, then tested for associations with concurrent changes in cardio-metabolic risk (CMR) scores and 14 biomarkers concerning body composition, glucose, insulin and lipid metabolism. Analyses were by mixed models, accounting for clustering (3 months, n=105–120; 12 months, n=80–97).

Results: Sitting reduction was significantly ($p<0.05$) associated only with lower systolic blood pressure at three months, and with CMR scores, weight, body fat, waist circumference, diastolic blood pressure, and fasting triglycerides, total/HDL cholesterol and insulin at 12 months. Significant differences between standing and stepping were only observed for systolic blood pressure and insulin; both favored stepping. However, replacing sitting with standing was significantly associated only with improvements in CMR scores, while replacing sitting with stepping was significantly associated with CMR scores and six biomarkers.

Conclusions: Improvements in several cardio-metabolic health risk biomarkers were significantly associated with sitting reductions that occurred in a workplace intervention. The greatest degree and/or widest range of cardio-metabolic benefits appeared to occur with long-term changes, and when increasing ambulatory activities.

Keywords: sedentary; compositional data analysis (CoDA); ambulation; intervention; biomarkers

TRIAL REGISTRATION: ACTRN1211000742976

1 **INTRODUCTION**

2 Increased risk of developing cardiovascular disease and diabetes (1), and elevated biomarkers of
3 risk for these chronic diseases (2), have been observed with high volumes of sitting time, and
4 especially sitting time accrued in a prolonged, continuous manner. Supporting the
5 epidemiological evidence, laboratory studies have shown acute benefits to glucose, insulin, and
6 lipid metabolism of interspersing long periods of sitting with even small amounts of activity (3-
7 5). Accordingly, interventions to reduce sitting, especially in the workplace — a key setting for
8 addressing prolonged sitting time — have been advocated as a public-health strategy (6, 7). In
9 particular, sit-stand workstations have emerged as effective tools in multi-component workplace
10 sitting interventions (8) as their usage reduces sitting time by large volumes.

11
12 By contrast with the clear evidence that such interventions can reduce sitting time, the evidence
13 concerning whether they are likely to impart non-acute benefits to cardio-metabolic health is less
14 clear, especially when sitting is primarily replaced with standing. Workplace sitting-reduction
15 interventions that primarily increase standing (e.g., through installation of sit-stand desks) have
16 shown benefits concerning lipid and glucose biomarkers, but inconsistently (9-11). Notably, thus
17 far, only the sitting-reduction interventions that have increased stepping (e.g., by use of treadmill
18 desks) have shown significant benefits to body weight or body composition (12, 13). The short-
19 term evaluations and insufficient sample sizes of most studies may explain the mixed findings.
20 However, it is also possible that the potential cardio-metabolic benefits of reducing sitting in an
21 intervention are inherently variable because participants can make a plethora of different
22 behavior changes when reducing sitting. Potentially relevant considerations include the volume

23 of sitting reduction, the activities replacing sitting (e.g., standing versus ambulatory activities),
24 and any compensatory activity changes that may or may not occur (14).
25
26 Recently, compositional data analysis (CoDA) has been used to simultaneously examine all
27 activities occupying a 24-hour day and test them in relation to cardio-metabolic biomarkers (15).
28 The study findings revealed that some biomarkers, notably those pertaining to glucose
29 metabolism, improve significantly when increasing light activity at the expense of sedentary time
30 (15). Importantly, CoDA is a valid method for examining data that sum to a fixed total, such as
31 24 hours (15) and it can be applied to evaluate all of the changes in activity that occur during an
32 intervention simultaneously, and test these in relation to changes in cardio-metabolic biomarkers.
33 To our knowledge, CoDA has not been applied in this context, nor to the examination of
34 standing as a separate component from ambulatory light activities. Using CoDA, we therefore
35 examined the associations of short- and long-term (3- and 12-month) changes in daily time use
36 with concurrent changes in cardio-metabolic biomarkers, within participants receiving the *Stand
37 Up Victoria* intervention.

38

39 **METHODS**

40 The *Stand Up Victoria* cluster-randomized trial was registered with the Australian New Zealand
41 Clinical Trials register (ACTRN12611000742976). The Alfred Health Human Ethics Committee
42 (Melbourne, Australia) granted ethical approval. Participants provided written consent. The
43 study was conducted in accordance with the CONSORT guidelines for cluster-randomized trials
44 (<http://www.consort-statement.org/>). Details are published elsewhere concerning the study

45 protocol (16), the measures used, development and pilot testing (10, 17), evaluation of the main
46 activity outcomes (18) and the secondary cardio-metabolic biomarker outcomes(19).

47

48 **Setting and participants**

49 Teams from study worksites that were at least one kilometre apart were identified and recruited
50 from a single organization, then were randomized to the intervention (n=7 sites, n=136 workers)
51 or control (n=7 sites, n=95 workers) condition. Eligibility criteria for individual participants in
52 the selected teams were: aged 18–65 years; not pregnant; ambulatory; speaks English; capable of
53 standing or sitting for ≥ 10 minutes continuously; and, working ≥ 0.6 full time equivalent with
54 designated access to a telephone, internet, and desk. Participants and study staff were not blinded
55 to group allocation. The present study evaluates only the intervention participants.

56

57 **Intervention**

58 The *Stand Up Victoria* intervention consisted of organizational support (senior management
59 support, a team champion who sent emails containing the intervention messages); environmental
60 modification (sit-stand workstations); and, individual health coaching (including goal setting and
61 tracking). [The intervention was tapered over 12 months with intensive components \(e.g., health
62 coaching, team champion intervention\) ceasing after 3 months.](#) It primarily targeted reductions in
63 workplace sitting time, especially sitting accrued for ≥ 30 minutes at a time continuously. The
64 main message was to “Stand Up, Sit Less, Move More”. The intervention encouraged
65 participants to replace part of their sitting across the entire day with standing and stepping, by
66 standing at their workstation for at least an hour a day, and by using a variety of self-selected
67 strategies, which might target standing, stepping or both. Evaluation of the study’s activity

68 outcomes previously revealed that, net of control, the intervention on average produced
69 moderately large effects on reduced sitting and increased standing (≈ 80 min/day at 3-months
70 and ≈ 40 min/day at 12-months) with no significant effect on stepping (-6 min/day at 12-months)
71 (18). These effects were established across the entire waking day (i.e., at work and outside of
72 work, considering the entire week rather than just workdays). Cardio-metabolic biomarker
73 outcomes, net of control, showed a significant improvement in overall cardio-metabolic risk and
74 fasting glucose at 12 months, and non-significant (but typically favorable) effects on the other
75 biomarkers (19).

76

77 **Data collection and measures**

78 Measurements were at baseline, three months into the intervention (upon completion of the
79 individual-level health coaching and champion emails) and at 12 months, and included an onsite
80 assessment [of biomarkers](#) and an activity monitoring assessment. [Further participant](#)
81 [characteristics were assessed using](#) ~~Online~~ questionnaires (LimeService:
82 www.limeservice.com) ~~assessed most other participant characteristics.~~

83

84 ***Cardio-metabolic biomarker outcomes***

85 The collection of these biomarkers is described in detail elsewhere(19), along with their changes
86 over the course of the intervention. The cardio-metabolic biomarkers examined were: systolic
87 blood pressure, diastolic blood pressure, weight, fat mass (kg, % of bodyweight), waist
88 circumference, fasting triglycerides, high-density lipoprotein (HDL)- and low density lipoprotein
89 (LDL)- cholesterol, total/HDL cholesterol ratio, glucose, insulin, insulin sensitivity (%S) and
90 steady state beta cell function (%B) as calculated using the homeostatic model assessment

91 (HOMA2) online calculator (<https://www.dtu.ox.ac.uk/homacalculator/>) version 2.2.3 and an
92 overall cardio-metabolic risk (CMR) score. CMR scores (20) were calculated by first log₁₀
93 transforming and normalizing (mean/SD) the relevant biomarkers, then by taking a weighted
94 average of their values: $1/5 \cdot \text{waist circumference} + 1/5 \cdot \text{triglycerides} - 1/5 \cdot \text{HDL-cholesterol} +$
95 $1/5 \cdot \text{fasting glucose} + 1/5 \cdot \text{mean of systolic and diastolic blood pressure}$. Changes in the
96 biomarkers were calculated as follow up score minus baseline score.

97

98 *Activity measures*

99 Activity was measured by the highly accurate (21) and responsive (22) activPAL3™ activity
100 monitor (PAL Technologies Limited, Glasgow, UK; minimum version 6.3.0). The waterproofed
101 monitor was secured onto the right anterior thigh with a hypoallergenic patch at the onsite
102 assessment. Each participant was asked to wear the monitor continuously (24 h/day) for the
103 following seven days, and to record the following times daily in a diary: starting and finishing
104 work; waking up; going to sleep (“lights out”); removing and re-attaching the monitor. Monitor
105 data were processed as reported in the primary outcomes paper (18). Though daily activities can
106 be classified in many ways, we subdivided time use by activity classifications consistent with the
107 intervention and measurement tool: sitting, standing, and stepping (during waking hours, while
108 wearing the monitor) and “other” time (non-wear time and time in bed).

109

110 **Statistical analyses**

111 Analyses were performed in STATA version 13 (STATA Corp, College Station, Texas, US) and
112 R version 3.3.0, using the packages “compositions” (“acomp” framework) “nlme” and
113 “lsmeans”. Statistical significance was set at $p < 0.05$, two-tailed. Missing data were excluded.

114

115 *Quantifying activity and activity change compositionally*

116

117 We used compositional methods, which have been outlined as applied to cross-sectional physical

118 activity and sedentary behavior data by Chastin et al (15). The total 24-hour day was divided

119 across four activities (stepping, standing, sitting, “other”). Sleep, other time in bed and non-wear

120 time comprised “other” time (i.e., 24 hours minus [monitored](#) waking hours). CoDA’s property of

121 “sub-compositional coherence” means that the exclusion of irrelevant activities does not

122 adversely affect results (23). The analysis includes only the sub-composition of activities that

123 comprise waking hours (stepping, standing, sitting); i.e., the composition of waking hours.

124 “Other” time was excluded in order to reduce the number of dimensions and provide efficient

125 estimates. This decision seemed to be reasonable since the “other” time was not targeted by the

126 intervention and did not change much over time at the group level or for individuals. At baseline,

127 three months, and 12 months, compositions were calculated using the R function “acomp”. No

128 method was required to address the problem of zero time use, as all participants spent some time

129 in every time-use category at each assessment. Compositional changes [Step_Δ, Stand_Δ, Sit_Δ] were

130 then measured by Aitchison’s perturbation method (23, 24). The ratios of each component in the

131 composition or sub-composition, such as $\left[\frac{\text{Step}_{12M}}{\text{Step}_{BL}}, \frac{\text{Stand}_{12M}}{\text{Stand}_{BL}}, \frac{\text{Sit}_{12M}}{\text{Sit}_{BL}} \right]$ for 12-month changes from

132 baseline, were calculated and were then divided by the sum total of these ratios. An equal

133 composition of these three activities at baseline and follow up would result in a compositional

134 change of [1/3,1/3,1/3]. Compositional changes were plotted as ternary diagrams (Figure 1), with

135 [key-some guide](#) values marked: no change; average sitting reduces by 1 h/16h day replaced with

136 either all stepping, all standing, or half of each; and, the average sitting reduces by 2 h/16h day
137 replaced entirely with standing.

138

139 *Quantifying associations of activity changes with biomarker changes*

140 The associations of activity changes with biomarker changes were examined as mixed models
141 (“lme” function), with a random intercept for cluster, and fixed effects for changes in the activity
142 composition [Step_Δ, Stand_Δ, Sit_Δ]. Short- and long-term changes were examined separately.

143 | Briefly, we used an isometric log-ratio transformation (i.e., “ilr” function) to measure the
144 | compositional change as two parameters (z1 and z2). These parameters are orthogonal and can
145 | therefore be safely included together as independent variables in the mixed models (15, 23). The
146 | isometric log-ratio transformation can be performed from a number of perspectives. The primary
147 | perspective we used allows for the effect of a decrease in the parameter z1 on biomarkers to
148 | indicate the effects of making sitting a smaller proportion of the waking day. These effects are
149 | estimated while controlling for shifts in the remaining non-sitting time between standing and
150 | stepping, the effect of which is measured as the parameter z2. The transformation was as
151 | follows:

$$z1_{Sit\ vs\ stand\ \&\ step} = \sqrt{\frac{2}{3}} \ln \left(\frac{Sit_{\Delta}}{\sqrt{Stand_{\Delta} \times Step_{\Delta}}} \right) [Eq. 1]$$

$$z2_{Stand\ vs\ step} = \sqrt{\frac{1}{2}} \ln \left(\frac{Stand_{\Delta}}{Step_{\Delta}} \right) [Eq. 2]$$

152

153 In addition, we presented selected estimates for the z2 parameter calculated from different
154 perspectives that indicate the effects of shifts in non-stepping time between sitting and standing

155 (more standing less sitting), and the shifts in non-standing time between sitting and stepping
156 (more stepping less sitting). Although the direction and significance of the parameters can be
157 used to understand the findings, the clinical relevance of the coefficients is not straightforward.
158 Estimates were presented partially standardized, with biomarker changes all expressed as a
159 number of baseline standard deviations, so that the relative effects on the different biomarkers
160 can be compared. To better understand the results, tertiles of predicted improvement (most
161 improved/least worsened to least improved/most worsened) were plotted across changes in the
162 composition that participants made (as presented in Figure 2). Also, to better indicate effect
163 sizes, the predicted mean improvement was calculated across a range of standing and stepping
164 changes in the composition that culminate in reducing sitting to recommended levels of 50%
165 (25). Consistent with the use of CoDA methods, our analyses did not adjust for total waking
166 | hours (or wear time). Instead, a sensitivity analysis using the composition of all [waking 24](#) hours
167 | was conducted to verify that excluding changes in “other” time was reasonable (and by
168 | implication that ignoring the total amount of waking hours was reasonable).

169

170 **RESULTS**

171 Baseline characteristics of intervention participants are shown in Supplemental Table 1. Relevant
172 data on short- and long-term changes were available from 105–120 participants (77–88%) and
173 80–97 (59–71%), respectively. Generally, those who provided data were similar to those who
174 dropped out, with the exception being that more women than men dropped out during the
175 intervention, which shifted anthropometric biomarkers in directions expected for a group
176 containing more males.

177

178 **Activity composition**

179 Activity outcomes have been reported previously (18). Considering activity as a composition of
180 daily time use, the intervention group's daily activity was very high in sitting, low in standing
181 and very low in stepping both at baseline [65.4%, 24.1%, 10.5%] and to a lesser extent at 12
182 months [60.4%, 29.5%, 10.1%] (Supplemental Figure 1), corresponding to a mean 12-month
183 change of [0.30, 0.39, 0.31]. Figure 1 is a ternary plot of the 12-month changes, with each corner
184 indicating a complete change towards that activity (from 0% to 100% of waking hours) and with
185 the centre indicating no change. Individual changes made by participants were highly variable.
186 The mean change in the composition was statistically significant (with the 95% confidence
187 region excluding no change) and was very close to the point indicating a drop in mean baseline
188 sitting of 1 hour/16 hours awake, when sitting is replaced exclusively with standing.

189

190 **Changes in the activity composition with changes in biomarkers**

191 Three-month sitting reductions were significantly associated only with changes in systolic blood
192 pressure ($p=0.039$), with the direction of associations indicating sitting reduction to be beneficial
193 (Tables 1–2). Long-term (12-month) sitting reductions were significantly associated with
194 improvements in CMR, triglycerides, total/HDL cholesterol ratio, diastolic blood pressure,
195 weight and body fat, waist circumference and insulin, and had a borderline significant ($p=0.063$)
196 association with improved insulin sensitivity (Tables 3–4).

197

198 In terms of the forms of sitting reductions associated with biomarker changes, overall CMR
199 scores improved significantly with sitting-standing substitutions ($p=0.031$) and with sitting-
200 stepping substitutions ($p=0.028$) without a statistically significant difference between standing

201 and stepping ($p=0.240$). By contrast, for fasting insulin and insulin sensitivity (HOMA-S),
202 stepping was significantly better than standing as a sitting replacement ($p=0.006$ and 0.032). No
203 significant effect on these biomarkers was seen of replacing sitting with standing ($p=0.889$ and
204 0.943) whereas replacing sitting with stepping was associated with significant benefit ($p=0.006$
205 and 0.029). Figure 2 displays the results graphically. CMR improvements were seen when
206 reducing the contribution of sitting to the overall waking day. At some levels of sitting change,
207 there was patterning whereby more CMR improvement was seen when the remaining time use
208 was shifted more towards stepping rather than standing (i.e., from left to right across the graph),
209 but this was not evident with the largest sitting reductions. All of the participants in the most
210 improved tertile of CMR had made sitting reductions. Figure 2b shows that the degree of
211 improvement that occurred at all levels of sitting change appeared dependent on how much of
212 the remaining (non-sitting) time use shifted towards stepping (most beneficial) versus standing.
213
214 For the other outcomes that had significantly improved with long-term sitting reduction (i.e.,
215 triglycerides, total/HDL cholesterol, diastolic blood pressure, weight, body fat (kg and %) and
216 waist circumference), it was not clear whether or not these improvements depended on sitting
217 being replaced with ambulatory activities. Suggestive that either standing or ambulation can
218 improve these outcomes, there was no significant difference whether sitting was replaced with
219 standing or stepping. However, the effects on these outcomes observed for replacing sitting with
220 standing did not reach statistical significance, while replacing sitting with stepping was
221 significantly associated with improved total/HDL cholesterol ratio ($p=0.045$), diastolic blood
222 pressure ($p=0.027$), and fat mass (kg and %, $p=0.034$ and 0.022). In addition to statistical
223 significance, the direction of the results, and the patterning of biomarker changes across activity

224 as plotted in Supplemental Figures 2–5, are informative. These were consistent with these
225 biomarkers improving somewhat by substituting sitting with standing and improving slightly
226 more by substituting sitting with stepping. Supplemental Table 2 shows the estimated mean 12-
227 month changes in cardio-metabolic outcomes when reducing baseline mean sitting (65.4%) to
228 desirable levels (50%) via various replacement strategies. Moderate to strong improvements
229 (0.5–0.8 SD) were seen for many outcomes but only with substantial increases in ambulation. In
230 order to see a small improvement in mean biomarkers (0.2 SD), only a small percentage of the
231 sitting reduction needed be achieved by increasing ambulatory activities for lipids and blood
232 pressure (20% or less), for insulin (21%) and for some of the adiposity indicators (waist
233 circumference and body fat percentage). The requirement for ambulation was higher for the other
234 outcomes, ranging from 30% to 68% of the sitting replacement.

235

236 Changes in the amount of “other” time relative to sitting standing and stepping were only
237 significantly associated with systolic blood pressure at 12 months, and triglycerides, HDL
238 cholesterol and HOMA-S at three months (Supplemental Table 3). For all these outcomes, the
239 conclusions concerning reducing sitting relative to standing and stepping, and shifts between
240 standing and stepping were no different whether examining all hours or only waking hours.

241

242 **DISCUSSION**

243 Previously, we showed the *Stand Up Victoria* workplace sitting-reduction intervention
244 predominantly reduced sitting by increasing standing (18), and was effective in the long term for
245 improving fasting glucose and an overall CMR score, net of control (19). The present study
246 extends from these findings to understand how the various activity changes that intervention

247 participants made were associated with concurrent biomarker changes, using a novel application
248 of compositional analysis. We found that sitting reduction was associated with significant
249 improvements in the biomarkers of cardiovascular and metabolic health across all of the areas
250 examined (glucose and insulin metabolism, lipid metabolism, blood pressure, body composition).
251 To varying degrees, the various benefits appeared to depend on the type of sitting reduction (i.e.,
252 whether sitting was replaced with standing or with stepping).

253

254 Both the previously reported outcomes of the workplace sitting intervention (19) and the present
255 findings may indicate the need for long-term intervention to improve biomarkers via sitting
256 reduction. We saw many significant associations of activity changes with biomarker changes
257 over a 12-month timeframe, and very few over a three-month period. While this could be a
258 chance finding, it could also reflect a physiological requirement for long-term behavior change in
259 order to improve these biomarkers. Either way, it appears prudent to investigate long-term
260 effects rather than infer them from short-term interventions, where benefits may be missed.

261

262 Our CMR findings showed that cardio-metabolic biomarker improvement can occur when
263 replacing sitting time with non-ambulatory activities. However, findings for the individual
264 biomarkers suggested the degree and/or range of cardio-metabolic biomarker improvements may
265 be greater when replacing sitting with ambulation than with standing. Fasting insulin and
266 HOMA-S improved significantly more by replacing sitting with stepping than with standing.
267 Some of the findings showed seemingly conflicting results whereby standing was neither
268 significantly beneficial, nor significantly inferior to stepping. This apparent conflict is potentially
269 explained by the study's sample size providing insufficient precision to distinguish standing from

270 either sitting or stepping, with standing having an impact that was more beneficial than sitting
271 but less beneficial than stepping. Larger RCTs or meta-analyses may yield further insights as to
272 potential benefits of replacing sitting with standing within field-based sitting-reduction
273 interventions. Cross-sectionally, in isothermal analyses, reallocating time use away from sitting
274 towards additional standing has shown significant beneficial associations with triglycerides,
275 HDL cholesterol, total/HDL cholesterol ratio and fasting glucose though not with weight or waist
276 circumference (26). In addition to the outcomes that appear important from the existing
277 literature, our findings suggest that key biomarkers that might be important to collect when
278 evaluating interventions similar to Stand Up Victoria are: those comprising CMR scores; those
279 showing the greatest response to substituting sitting specifically with standing (i.e., waist
280 circumference, fasting glucose, triglycerides and diastolic blood pressure, whose coefficients for
281 sitting versus standing were largest at ≈ 0.3 to 0.6 SD); and, the biomarkers that showed the most
282 predicted improvement when reducing sitting to desirable levels (25) without large changes to
283 stepping (i.e., lipids, blood pressure, insulin, waist circumference and body fat).

284

285 Consistent with our findings, the underlying biological mechanisms would also tend to suggest
286 that both standing and stepping should be beneficial, but with the greatest benefit for stepping.
287 The added benefit for glycemic control associated with transitions to stepping compared with
288 transitions to standing may reflect greater muscle and/or metabolic activity in general (27, 28), or
289 the comparatively higher energy demand associated with activation of fast-twitch glycolytic
290 fibres (29, 30). This contrasts with the lesser glycemic benefit of transitions to standing which
291 involve a comparatively lower energy requirement and engagement of oxidative fibres, favoring
292 fat metabolism (29, 30). Broadly, the findings aligned with recent acute experimental studies in

293 overweight adults that have sometimes indicated greater improvements in postprandial glucose
294 and insulin responses (4, 31, 32) by interrupting sitting with intermittent ambulation compared
295 with standing breaks. Similarly, cross-sectional isothermal analyses have also showed stronger
296 effects on a range of cardio-metabolic biomarkers when sitting time is reallocated to additional
297 stepping rather than standing (26). Notably “stepping” is an amalgamation of various
298 ambulatory activities, and the stepping findings are therefore reflective of the “[averagetypical](#)
299 [mix](#)” of the various ambulatory activities that were performed by the participants of the *Stand Up*
300 *Victoria* intervention, which had a predominant focus on light-intensity activity. [Within the](#)
301 [stepping category, effects of running are likely greater than walking slowly, for example.](#)
302 [Similarly, effects of sitting are reflective of the “typical mix” of sitting for this population; it is](#)
303 [possible that certain types of sitting \(e.g., sitting in long bouts, sitting after lunch\) are more](#)
304 [deleterious than others.](#)

305
306 Strengths of the study include the evaluation of the short- and long-term effects on objectively
307 assessed biomarkers alongside accurately and objectively measured behaviors, with good study
308 retention especially in the short term. A novel element was that this intervention that targeted
309 whole-of-day behavior changes was examined with analytic methods suited to such data. A key
310 limitation was that the study was not powered a priori for this secondary analysis and showed
311 evidence of limited power and precision (e.g., the wide margins of error around predicted mean
312 values). We did not adjust for co-occurring changes in the intervention (e.g., in dietary intake) as
313 these are potentially attributable to the intervention; however, the changes may have been
314 coincidental, and therefore our results may be subject to confounding. It appeared unlikely that
315 the findings were strongly affected by unexamined activities or variation in total waking hours.

316 However, this is impossible to verify without accurate and detailed measures (e.g., high-quality
317 sleep, time in bed unable to sleep etc.) or knowledge of activity during unobserved time. Another
318 limitation was that the study took neither measures of post-prandial metabolism nor continuous
319 biomarker measurements in the behavior setting (e.g., by continuous glucose monitoring or 24-
320 hour ambulatory blood pressure monitoring). A focus on the postprandial state may be especially
321 important for interventions targeting not only whole-of-day changes but also workplace changes,
322 since the postprandial periods after lunch and other meals are often spent at work.

323 Generalizability is limited, as participants were recruited non-randomly from a single
324 organization and there was some evidence of a tendency to disproportionately lose women to
325 follow-up. Also, our sample was a general population of workers; effects may also differ within
326 clinical populations.

327

328 In conclusion, our study provides further insights into the heterogeneous findings of studies
329 examining the cardio-metabolic benefits of reducing sitting time. Firstly, long-term intervention
330 seems necessary to identify relevant changes. Secondly, if using primarily sitting-standing
331 substitutions, these seemingly need to be large volume, and achieved without adversely
332 impacting stepping. Finally, sitting should be replaced with ambulatory activity if benefits to
333 fasting insulin levels are desired and for potentially greater benefits to other biomarkers as well.

334

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List of Figures: Figure Captions

Figure 1: Change in the composition of the waking day between baseline and 12 months. The centre shows no change, and each corner is a complete change in the activity (from 0% to 100% of the waking day).

Figure 2: Predicted improvement in overall cardio-metabolic risk score (a, left) and insulin (b, right) by changes in the waking day's composition (12 months).

List of Supplementary Digital Content

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