A 2-wk reduction of ambulatory activity attenuates peripheral insulin sensitivity

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1Centre of Inflammation and Metabolism at Department of Infectious Diseases and Copenhagen Muscle Research Centre, Rigshospitalet, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark; 2Harry S. Truman Memorial Veterans Hospital, Health Activity Center, Departments of Nutrition and Exercise Physiology and Internal Medicine, University of Missouri, Columbia, Missouri; and 3Health Activity Center, Departments of Biomedical Sciences and of Medical Pharmacology and Physiology, University of Missouri, Columbia, Missouri

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Krogh-Madsen R, Thyfault JP, Broholm C, Mortensen OH, Olsen RH, Mounier R, Plomgaard P, van Hall G, Booth FW, Pedersen BK. A 2-wk reduction of ambulatory activity attenuates peripheral insulin sensitivity. J Appl Physiol 108: 1034–1040, 2010. First published December 31, 2009; doi:10.1152/japplphysiol.00977.2009.—US adults take between ~2,000 and ~12,000 steps per day, a wide range of ambulatory activity that at the low range could increase risk for developing chronic metabolic diseases. Dramatic reductions in physical activity induce insulin resistance; however, it is uncertain if and how low ambulatory activity would influence peripheral insulin sensitivity. We aimed to explore if healthy, nonexercising subjects who went from a normal to a low level of ambulatory activity for 2 wk would display metabolic alterations including reduced peripheral insulin sensitivity. To do this, ten healthy young men decreased their daily activity level from a mean of 10,501 ± 808 to 1,344 ± 33 steps/day for 2 wk. Hyperinsulinemic-euglycemic clamp. In addition, we show evidence that reduced ambulatory activity would negatively impact lean mass of legs, cardiovascular fitness, and lean leg mass. Reduced ambulatory activity significantly lowers both lean body mass and cardiorespiratory fitness.

Epidemiological evidence indicates that low physical activity plays a causal role in the development of Type 2 diabetes (11, 12, 17). Our longer-term hypothesis is that reductions in daily ambulatory activity levels (reduced steps taken throughout the day) initiate attenuation in skeletal muscle insulin sensitivity that precedes a later development of overt insulin resistance. It is estimated that most free-living, nonexercising US adults take between ~2,000 and ~12,000 steps per day, a wide range of ambulatory activity that at the high range may decrease risk and at the low range may increase risk for developing chronic metabolic disease(s) (4). We postulated that healthy, nonexercising subjects who transitioned from a high to low level of ambulatory activity (from >10,000 to <2,000) would quickly display metabolic alterations. Our initial findings showed that healthy young men who reduced their daily steps from an average of 10,501 ± 808 to 1,344 ± 33 for a 2-wk period displayed a clustering of metabolic alterations including increased insulin response to an oral glucose tolerance test (OGTT), increased plasma triglyceride response to an oral fat tolerance test, and a 7% increase in visceral fat (21). These findings led us to question if the loss of insulin sensitivity induced by reduced ambulatory activity was due to peripheral or hepatic decreases in insulin sensitivity. Moreover, if there was a decline in peripheral insulin sensitivity we questioned if it was associated with reduced activation of the insulin signaling pathway in skeletal muscle as has been shown in rodent models in which daily physical activity was ceased for acute periods of time (16). We additionally wished to determine if reduced ambulatory activity would negatively impact lean body mass or cardiorespiratory fitness [maximal oxygen consumption (VO2 max), two factors strongly linked to metabolic health and mortality risk. Herein we provide evidence that 2 wk of reduced daily ambulatory activity in healthy young, nonexercising subjects decreases peripheral insulin sensitivity and insulin stimulation of Akt in skeletal muscle without change in rate of glucose appearance during a hyperinsulinemic-euglycemic clamp. In addition, we show evidence that reduced ambulatory activity significantly lowers both lean body mass and cardiorespiratory fitness.

METHODS

Ethical approval. All subjects gave oral and written consent, and the study was approved by the Scientific-Ethics Committee of Copenhagen and Frederiksborg Municipalities (file no. KF01268925) in accordance with the Helsinki Declaration.

Subjects. Ten healthy human males (mean age 23.8 ± 1.5; body mass index of 22.1 ± 0.7 kg/m2) participated in the study [reported in a preliminary report (21)]. Before the study all 10 subjects underwent a thorough clinical examination. All subjects were nonsmokers, asymptomatic, with no family history of diabetes, did not take medications, and revealed no physical abnormalities during examination. All subjects had normal resting values of blood pressure, normal plasma levels of glucose, insulin, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (TG), normal hematological parameters including leukocyte counts, and normal hepatic, thyroid, and renal

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parameters. None of the participants performed planned exercise sessions of >2 h/wk or walked <3,500 steps/day.

**Study design.** In a free-living environment, participants were instructed to nightly record their daily steps (cycling not included) for 1 inclusion-week and then reduce steps to 1,500 per day for 14 days (cycling not allowed). Step number was measured using a simple pedometer (Yamax Digi-Walker SW-200, London, UK); daily physical activity was also monitored by an Actiheart monitor (Cambridge, UK). Subjects did not exercise more than 2 h/wk on a recreational level. Subjects who walked less than 3,500 steps per day or performed regular exercise were excluded. All subjects agreed to refrain from vigorous physical activity and only performed physical activity corresponding to their normal routines, for 2 days preceding the first test day. The number of steps was registered every night at bedtime. Dietary records were taken during the inclusion-week. The subjects carefully noticed what they consumed day by day, and they maintained their usual dietary habits during the whole study. Subjects were not allowed to consume alcohol 2 days preceding the first test and during the study period. Participants agreed to weigh and register consumed food the day before pre- and post-insulin clamp and the $\dot{V}O_2_{max}$ tests. Figure 1 illustrates testing times.

**Determinations.** An incremental exercise test was performed on a cycle ergometer (Monark 839E, Monark Ltd, Varberg, Sweden) to obtain $\dot{V}O_2_{max}$ for each participant with indirect calorimetry system (Moxus modular $V_2$ system, AEI Technologies, Pittsburgh, PA) as previously described (1). Preceding the study, subjects performed a familiarization test.

The Actiheart monitor [used to measure daily energy expenditure (7)] is attached to the chest with two standard electrocardiogram (ECG) electrodes and is able to measure acceleration, heart rate (HR), HR variability, and ECG magnitude for epoch settings of 15, 30, and 60 s and can be recorded for a set time. Data on interbeat intervals (IBI logging) and ECG waveforms can also be recorded. Acceleration is measured by a piezoelectric element within the Actiheart with a frequency range of 1–7 Hz (3 dB). For every participant, the Actiheart monitor was tested for adequate HR pickup by recording ECG waveforms for ~30 s before the rest test. If pickup was adequate, the Actiheart was set up to record HR and movement continuously for 1 wk, after which it was reloaded for the rest of the study period.

Fat and fat-free tissue masses for the whole body, trunk, and extremities were measured using a dual-energy X-ray absorptiometry (DXA) scanner, Lunar Prodigy Advance (GE Healthcare, Madison, WI) (21).

Hyperinsulinemic-euglycemic clamps were performed after an overnight fast (Fig. 1). Peripheral catheters were placed in an antecubital vein for blood sampling, in the contralateral antecubital vein for infusion of glucose, insulin, and stable isotopes, and in a dorsal hand vein for blood sampling; the catheterized hand was wrapped in a heating blanket to obtain arterialized venous blood for measurement of glucose and potassium during the clamp. The experiment was commenced by priming the glucose pool by administrating a bolus of 17.5 μmol/kg of [6,6-2H2]glucose (Cambridge Isotopes Laboratories). This was followed by a continuous infusion (rate 0.4 μmol·kg⁻¹·min⁻¹) for 2 h before the start of the clamp.

Insulin (Actrapid, Novo Nordisk Insulin, 100 IE/ml) was infused continuously at a rate of 40.0 mU·min⁻¹·m⁻², and the plasma glucose concentration was kept at 5.0 mM by a coinfusion of glucose (200 g/1,000 ml, enriched with [6,6-2H2]glucose to 2.5%) at a variable rate. During the 4-h clamps the infusion rate of [6,6-2H2]glucose was reduced to 0.08 μmol·kg⁻¹·min⁻¹. Arterialized blood was analyzed...
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for glucose and potassium concentrations at intervals of 5 min during the first hour, and every 10 min during the last 3 h of the clamp. Blood samples were collected in heparin-containing tubes and immediately centrifuged for 15 min at 3,500 rpm, and the plasma was stored at −20°C until further analysis.

The plasma glucose enrichment was measured as previously described (23). The glucose turnover rate of appearance (Ra) and rate of disappearance (Rd) were calculated assuming steady state:

\[ Ra = \frac{F_{\text{infusion}}}{\text{E}_{\text{glucose}}} \]

\[ Rd = \frac{F_{\text{total}}}{GIR} - \frac{F_{\text{total}}}{\text{E}_{\text{glucose}}} \]

where \( F_{\text{infusion}} \) is the infusion rate of glucose tracer (\( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)) in terms of lean body mass; \( F_{\text{total}} \) is the enrichment of glucose in plasma; \( E_{\text{glucose}} \) is the sum of \( F_{\text{infusion}} \) and the \([6,6-\text{H}_2]\) glucose infused by the clamp; GIR is the glucose infusion rate; and kilograms refers to lean body mass.

Baseline blood samples were obtained before initiation of the stable isotope infusion (time point −2 h, Fig. 1). Glucose, triglyceride (TG), and free fatty acids (FFA) were measured with an automated analyzer (Cobas Faro, Roche, Basel, Switzerland); insulin and C-peptide by ELISA (DAKO, Glostrup, Denmark); tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-15, and leptin by ELISA (R&D Systems); and adiponectin by a RIA kit (LINCO Research).

Vastus lateralis muscle biopsies were taken before and 1 and 4 h after the starting of the clamp. Muscle was quickly frozen in liquid nitrogen and stored at −80°C until later analysis. Muscle tissue was homogenized in ice-cold buffer containing protease inhibitors and phosphatase inhibitors as previously referenced (13, 29). Insulin receptor β (IRβ), phosphorylation of Akt at threonine 308 (pAktthr308), total Akt, phosphorylation of AS160 (pAS160), and AS160 total content were performed as referenced previously (29). Regarding tyrosine phosphorylation of IRβ (pTyIRβ), muscle homogenate was incubated overnight with anti-phosphotyrosine agarose beads (Sigma). Both immunoprecipitates and muscle homogenates were separated by SDS-PAGE and transferred to PVDF membranes before probing with appropriate antibodies. The protein bands were detected using Supersignal West Femto (Pierce, Rockford, IL, USA) or enhanced chemiluminescence (Amersham Biosciences, UK) and quantified using a signal West femto (Pierce, Rockford, IL, USA) or enhanced chemiluminescence (Amersham Biosciences, UK) and quantified using a signal West femto (Pierce, Rockford, IL, USA) or enhanced chemiluminescence (Amersham Biosciences, UK).

Statistical analyses. Data were tested for normal distribution by the Kolmogorov-Smirnov test. Variables were analyzed using parametric methods (paired t-tests; pre vs. post) on the absolute data, and reported values are means ± SE. Correlations were determined with a Pearson correlation test. All Western blots were normally distributed when log-transformed before analysis and then analyzed using parametric methods and expressed as geometric mean (95% confidence interval). Within-subject variation over time and variation between trials were analyzed using repeated-measures (2-way ANOVA, time-by-trial). If a significant interaction (time × trial) was found, Bonferroni-corrected P values were obtained as appropriate to identify significant differences between trials and to identify significant differences from baseline values. \( P < 0.05 \) was considered statistically significant. Analysis was performed using a statistical software package (SAS version 9.1.3 SAS Institute).

RESULTS

Pedometer and Actiheart data. For a 2-wk period, participants reduced the number of daily steps by more than 85% from a baseline of ∼10,000 per day, as published previously (21), resulting in reduced energy expenditure (kJ/day; estimated by Actiheart) from a mean of 5,020 ± 515 to 3,010 ± 294 kJ/day. The decline in number of steps from baseline to 2 wk significantly correlated with the decline in daily energy expenditure (kJ/day) (\( r = 0.922; P = 0.001 \)), and decline in \( \dot{V}_{\text{O}2\text{max}} \) (ml/min) (\( r = 0.960; P = 0.001 \)) or \( \dot{V}_{\text{O}2\text{max}} \) (ml·min\(^{-1} \cdot \text{kg}^{-1} \)) (\( r = 0.921; P < 0.01 \)) (Table 1).

Cardiovascular fitness and body composition (DXA). A significant 7.2% and 6.6% decline was observed in \( \dot{V}_{\text{O}2\text{max}} \) (ml·min·kg\(^{-1} \)·min\(^{-1} \)) and total body mass (10). Regarding tyrosine receptor phosphorylation, a Pearson correlation test. All Western blots were normally distributed when log-transformed before analysis and then analyzed using parametric methods and expressed as geometric mean (95% confidence interval). Within-subject variation over time and variation between trials were analyzed using repeated-measures (2-way ANOVA, time-by-trial). If a significant interaction (time × trial) was found, Bonferroni-corrected P values were obtained as appropriate to identify significant differences between trials and to identify significant differences from baseline values. \( P < 0.05 \) was considered statistically significant. Analysis was performed using a statistical software package (SAS version 9.1.3 SAS Institute).

Table 1. Correlation coefficients

<table>
<thead>
<tr>
<th>( \Delta )Daily Steps</th>
<th>( \Delta )Physiological Variables</th>
<th>( r )</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta )Daily energy expenditure, kJ/day</td>
<td>0.922</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>( \Delta \dot{V}_{\text{O}2\text{max}} ) (ml·kg(^{-1} )·min(^{-1} ))</td>
<td>0.921</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>( \Delta \dot{V}_{\text{O}2\text{max}} ) (ml/min)</td>
<td>0.960</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>( \Delta \dot{C} \text{EE} ) (mg·kg(^{-1} )·min(^{-1} ))</td>
<td>0.262</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>( \Delta \dot{V}_{\text{O}2\text{max}} ) (ml·min·kg(^{-1} ))</td>
<td>−0.225</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Pearson correlation coefficients (\( r \)) are given between \( \Delta \) in daily steps and \( \Delta \) in physiological variables, where \( \Delta \) represents a decrease from pre- to postintervention. No other but the mentioned factors correlated. \( \dot{V}_{\text{O}2\text{max}} \), maximal oxygen consumption; NS, nonsignificant; \( n = 10 \).

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et al. muscle TNF mRNA and protein expression (data not shown) were not affected by 2 wk of reduced daily stepping.

**DISCUSSION**

Major novel findings of this study were that 2 wk of reduced daily ambulatory activity in a free-living condition resulted in decreases in insulin-stimulated muscle Akt phosphorylation, peripheral insulin sensitivity, leg lean mass, and $V\dot{O}_{2\text{max}}$ in young healthy men who had not been previously exercise trained. As shown by others in previous studies, the later three aforementioned decreases are primary decrements that can lead to chronic metabolic disorders and premature mortality.

Importantly, the experimental design, used here, models the extremes [~2,000 to ~12,000 (4)] in numbers of daily steps in the majority of free-living adults in developed countries, most of whom do not partake in structured exercise programs (4). Therefore, the present study is distinctly different from previous studies in which nontypical and extreme changes in activity levels were deployed including continuous bed rest in which subjects are not allowed to stand or walk (8) and detraining studies in which intense structured-exercise programs ceased (2, 18). Furthermore, subjects served as their own control, eliminating potential gene differences that might occur by comparing separate groups of active and less active subjects.

The attenuation of peripheral insulin sensitivity after 2 wk of the decreased ambulatory activity occurred without any detectable alteration in endogenous hepatic glucose production, implying that a peripheral decrement in insulin sensitivity is primary to hepatic insulin resistance on reductions in daily stepping. These findings further reinforce the dogma that glucose entry is exquisitely matched with substrate usage in skeletal muscle, in part by modulating muscle insulin sensitiv-

### Table 2. Pre- and post-2-wk intervention results

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Preintervention</th>
<th>Postintervention</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V\dot{O}_{2\text{max}}$, test</td>
<td>Mean</td>
<td>SE</td>
<td>Mean</td>
</tr>
<tr>
<td>$V\dot{O}_{2\text{max}}$, ml/min</td>
<td>3,435</td>
<td>149</td>
<td>3,194</td>
</tr>
<tr>
<td>$V\dot{O}_{2\text{max}}$, ml·min$^{-1}$·kg$^{-1}$</td>
<td>47.7</td>
<td>1.3</td>
<td>45.1</td>
</tr>
<tr>
<td>Maximal power, W</td>
<td>259</td>
<td>11</td>
<td>243</td>
</tr>
<tr>
<td>Maximal HR, beats/min</td>
<td>194</td>
<td>3</td>
<td>193</td>
</tr>
<tr>
<td>DXA scan</td>
<td>Total body mass, kg</td>
<td>70.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Trunk lean mass, kg</td>
<td>26.3</td>
<td>0.8</td>
<td>25.6</td>
</tr>
<tr>
<td>Arm lean mass, kg</td>
<td>6.7</td>
<td>0.3</td>
<td>6.7</td>
</tr>
<tr>
<td>Leg lean mass, kg</td>
<td>18.6</td>
<td>0.5</td>
<td>18.1</td>
</tr>
<tr>
<td>Plasma</td>
<td>Glucose, mmol/l</td>
<td>5.39</td>
<td>0.11</td>
</tr>
<tr>
<td>Insulin, pmol/l</td>
<td>31.9</td>
<td>3.7</td>
<td>31.8</td>
</tr>
<tr>
<td>C-peptide, pmol/l</td>
<td>337.6</td>
<td>27.5</td>
<td>335.4</td>
</tr>
<tr>
<td>FFA, mmol/l</td>
<td>1.001</td>
<td>199</td>
<td>1.266</td>
</tr>
<tr>
<td>TG, μmol/l</td>
<td>617</td>
<td>56</td>
<td>647</td>
</tr>
<tr>
<td>TNF, pg/ml</td>
<td>1.31</td>
<td>0.13</td>
<td>1.38</td>
</tr>
<tr>
<td>IL-6, pg/ml</td>
<td>0.79</td>
<td>0.22</td>
<td>1.02</td>
</tr>
<tr>
<td>IL-15, pg/ml</td>
<td>1.29</td>
<td>0.1</td>
<td>1.27</td>
</tr>
<tr>
<td>Adiponectin, ng/ml</td>
<td>5,056</td>
<td>803</td>
<td>4,841</td>
</tr>
<tr>
<td>Leptin, pg/ml</td>
<td>2,334</td>
<td>389</td>
<td>2,676</td>
</tr>
</tbody>
</table>

$V\dot{O}_{2\text{max}}$ test results, dual-energy X-ray absorptiometry (DXA) scans, and plasma concentrations on lipid and glucose metabolism as well as inflammation are shown. Total lean mass decreased significantly post-2 wk intervention vs. preintervention (see Ref. 21). HR, heart rate; FFA, free fatty acids; TG, triglycerides. $n = 10$. 

Although the evidence that acute exercise protocols dramatically improve insulin sensitivity (10, 27). However, the ability of increased physical activity (7 days of exercise) to improve insulin sensitivity is blocked if subjects are maintained in an energy balance by consuming postworkout calories that match the amount of calories expended in each daily exercise bout (3). This evidence strongly suggests that the ability of increased activity to improve insulin action is linked to acutely induced energy deficits. Because the subjects in the present study maintained the same caloric intake but dramatically lowered their daily activity it is likely that they were in a state of positive energy balance. This concept is contradicted by the evidence that subjects had a 1.6% reduction in total body mass. That being said, if the subjects were in a positive energy balance, it is likely that this excess energy played a role in the loss of peripheral insulin sensitivity after reduced stepping. A followup study could examine this link by having one group of subjects consume a reduced caloric intake that matches the reduction in energy expenditure that occurs after reducing daily stepping from 12,000 to 2,000 steps. This type of design would not only help to define the role of energy balance on insulin resistance induced by reduced stepping but would also help to determine the impact of positive energy balance on the loss of total body mass and lean body mass that was witnessed.
insulin sensitivity in human and animal models is very strong, it remains underappreciated as an initiator of metabolic disease and an underused model to study initial declines in insulin sensitivity that likely precede overt insulin resistance. The most common experimental model for studying insulin resistance is acute and long-term high-fat diets, which, as we have already stated, appear to be effective in sedentary conditions only. A recent study by Brons et al. (5) showed that a 5-day

Fig. 2. Glucose values during hyperinsulinemic-euglycemic clamp. A: glucose infusion rate (GIR) during the euglycemic clamp. B: blood glucose concentration just before (time point 0) and during the euglycemic clamp. C: area under the curve (AUC) for glucose rate of appearance (Ra) and rate of disappearance (Rd) during the euglycemic clamp (120–240 min). *Significant difference between preintervention (Pre) and postintervention (Post) (paired t-test, \( P = 0.01 \)). Preintervention is before reduced daily steps; postintervention is final 3 days of 14-day period of reduced daily steps. ● Preintervention determination; ■ postintervention determination; filled bars, preintervention determination; open bars, postintervention determination. Data are presented as mean ± SEM. \( n = 10 \).

Fig. 3. Insulin signaling in skeletal muscle during hyperinsulinemic-euglycemic clamp. Akt, AS160, and insulin receptor (IR)-\( \beta \)-protein content and phosphorylation (p) were examined in biopsies taken from vastus lateralis muscle pre- and post-euglycemic clamp. Muscle biopsies were obtained at time points 0 h (before insulin clamp) and 1 h and 4 h (after initiation of insulin clamp); labels on x-axis indicate these times. Labels on y-axis indicate: phosphorylation of IR\( \beta \) expressed relative to IR\( \beta \) protein (A); phosphorylation of Akt at threonine308 expressed relative to Akt protein (B); phosphorylation of AS160 expressed relative to AS160 protein (C); and representative immunoblots of signaling proteins. pTYIR\( \beta \), tyrosine phosphorylated IR\( \beta \). Data are expressed as geometric means (95% confidence interval). *Post hoc analysis, \( P = 0.03 \) (difference between pre- and postintervention). **Post hoc analysis, \( P < 0.05 \) (different from 0 h). \( n = 10 \).
high-fat/high-calorie diet in young healthy men (daily activity levels were not reported) induced hepatic but not peripheral insulin resistance measured by a hyperinsulinemic-euglycemic clamp. This suggests that diet-induced insulin resistance may initially be activated through hepatic disturbances while reductions in activity lead to declines in skeletal muscle insulin sensitivity. Type 2 diabetes has been linked to both increased consumption of dietary fats and a sedentary lifestyle, making it plausible that both of these lifestyle factors work in parallel to impair both hepatic and skeletal muscle insulin sensitivity and are an underlying feature of the dramatic increase in rates of Type 2 diabetes.

The loss of 2.8% in leg lean mass with 2 wk of reduced daily ambulatory activity was unanticipated as most literature suggests that reduced muscle loading must be drastic, such as limb immobilization or bed rest, to observe muscle atrophy. Thus it is likely that decreases in leg lean mass and in the rate of glucose disappearance per kilogram of whole body lean mass (Fig. 2C) both contribute to decreased glucose infusion rate in a hyperinsulinemic-euglycemic clamp (Fig. 2A) after 2 wk of reduced ambulatory activity.

A 7% suppression of cardiovascular fitness (V\(^{\text{O2 max}}\)) after lowered ambulatory activity was also unanticipated based on our notion that the loss in ambulatory activity would be of insufficient magnitude and duration to produce a loss. Because of the previously established strong connection between reduced cardiorespiratory fitness and premature mortality, the rapid decline in V\(^{\text{O2 max}}\) is clinically significant in these young, healthy subjects after only 2 wk of reduced stepping.

The parallel losses of peripheral insulin sensitivity, leg lean mass, and V\(^{\text{O2 max}}\) are clinically relevant as all three independently increase mortality. While low cardiovascular fitness is the best predictor of mortality (28), low skeletal muscle strength also increases mortality (20), and insulin resistance is believed to be a primary initiator of many chronic diseases (24), which also increase mortality. Taken together, we speculate that reduced ambulatory activity may be primary and predispose to other environmental–gene interactions, especially in at-risk populations such as overweight, elderly, or genetically predisposed humans, that lead to the early development of chronic diseases and/or premature mortality. Chronic diseases take years to become overtly clinical. Our observations suggest that reductions in daily steps or physical activity may initiate or contribute to progressive declines in metabolic function.

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DISCLOSURES

No conflicts of interest are declared by the authors.

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