Effect of contrasted levels of habitual physical activity on metabolic flexibility

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Bergouignan A, Antoun E, Monken I, Schoeller DA, Gauquelin-Koch G, Simon C, Blanc S. Effect of contrasted levels of habitual physical activity on metabolic flexibility. J Appl Physiol 114: 371–379, 2013. First published December 13, 2012; doi:10.1152/japplphysiol.00458.2012.—The factors regulating the body’s ability to switch from fat to carbohydrate oxidation in response to fuel availability changes, or metabolic flexibility (MF), are currently intensively investigated in the context of metabolic diseases. Although numerous metabolic diseases are associated with sedentary behaviors and metabolic inflexibility, the effect of habitual physical activity level (PAL) on MF regulation is surprisingly poorly known. We investigated how PAL affects MF in cross-sectional and interventional studies. MF was assessed in 44 subjects: normal-weight and overweight sedentary men submitted to 2 mo of exercise at current recommendations, normal-weight active men submitted to 1 mo of reduced PAL and normal-weight women submitted to 1 mo of bed rest, with or without exercise. MF was evaluated, before and after interventions, following two standard meals as the relationship between individual mathematical variances in insulin and nonprotein respiratory quotient (NPRQ) daily kinetics. Daily NPRQ and insulin variances differed according to habitual PAL (P = 0.002 and P = 0.009, respectively); active subjects had higher variances in NPRQ for lower variances in insulin than sedentary subjects, indicating a better MF. Detraining increased insulin variance (P = 0.009) and decreased NPRQ variance (P = 0.003), while training tended to have opposite effects. Insulin and NPRQ variances were negatively related along the PAL continuum (R² = 0.70, P < 0.001). Variance in NPRQ was also positively related to PAL (R² = 0.52, P < 0.001). By assessing MF with mathematical surrogates in conditions of daily pattern in meal’s intake, we showed that habitual PAL is associated with MF status, and that MF is modulated by changes in PAL.

Metabolic flexibility is defined as the body’s ability to adapt fuel oxidation to changing fuel availability and energy demand (21, 22). A metabolic deregulation that switches fuel preference toward glucose during fasting (11) and impairs the capacity to switch between fat and glucose as the primary fuel source after a meal (11) and during stimulated conditions, such as β-adrenergic stimulation or exercise (6, 7), has, however, been associated with metabolic disorders, such as obesity, insulin resistance, and type 2 diabetes. Such impaired capacity to switch between fuel utilization is defined as metabolic inflexibility. Although metabolic flexibility is gaining increasing recognition as a core component of metabolic health (14), the factors triggering a metabolically inflexible status are poorly known. To understand the causes of the development of metabolic flexibility will help to understand the etiology of metabolic diseases and can also provide insights for refining strategies of treatment.

Metabolic inflexibility may be favored by lifestyle factors, such as sedentary behaviors and high fat, energy-dense diet (11). During the shift to isoeenergetic high-fat diet, Smith et al. (27) showed that the ability of lean men to adjust fat oxidation was related to physical fitness and fasting insulin concentration. Combined with weight loss, exercise training improves insulin sensitivity (23), fasting fat oxidation, and increases mitochondrial content (15). Training without weight loss increases the activity of muscle oxidative enzymes and fat oxidation (13). Although the evidence that exercise per se affects insulin sensitivity independent of body mass loss is not straightforward (30), this body of data indirectly suggests that metabolic flexibility might be improved with regular exercise (11). Nevertheless, as highlighted recently (14), the effect of physical activity level (PAL) on metabolic flexibility has yet to be clarified. The objective of this study was thus to investigate 1) whether metabolic flexibility varies in groups of subjects with different habitual physical activity patterns, and 2) whether physical activity training/detraining interventions can modulate metabolic flexibility.

The assessment of metabolic flexibility is, however, not clearly established. Numerous definitions of metabolic flexibility can be found in the literature, and there is no standard method to apply. A common agreement is that it can be determined during challenging situations. Most of the previous studies used the method of the euglycemic-hyperinsulinemic clamp, because it allows performance of measurements in a controlled environment (14). However, such pharmacological invasive condition does not reflect the dynamic of meal-to-meal physiological responses. Other approaches have been used to assess metabolic flexibility, such as changes between fasting and postprandial respiratory quotient (RQ) (18) and the area under the curve of RQ following meal ingestion (10). However, fasting RQ has been shown to be a weak indicator of lipid oxidation capacity, since it is greatly influenced by energy

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balance and dietary macronutrient composition of the meals consumed on the previous days (14).

To investigate how physical activity modulates metabolic flexibility, we considered an approach based on the dynamic nature of daily postprandial metabolic responses to standardized meals rather than on RQ changes in response to supraphysiological doses of insulin during a clamp, or in response to high-fat/carbohydrate meal or diet. Based on the above definition of metabolic flexibility, we used an index that accounts for the daily postprandial relationship between RQ and insulin. This index was established from the overall intraindividual variances in the insulin and nonprotein RQ (NPRQ) responses to standard meals. A sedentary metabolically inflexible subject was hypothesized to be characterized by a large daily variance in insulin for a small variance in NPRQ, i.e., a small shift in the fuel mix being oxidized at a high insulin signal. The direct corollary is that improvement in metabolic flexibility by exercise training will increase the daily variance in NPRQ and decrease the daily variance in insulin. We took advantage of two of our studies investigating the effects of very contrasted interventions on physical activities (training, detraining, bed rest) on dietary fat metabolism, in subjects already segregated at baseline based on their habitual PAL (trained, untrained) and body mass (normally weight and overweight).

Between-study comparison was made possible because the main outcomes of WISE were previously fully detailed (3, 5). LIPOX main outcomes are not yet published, but methodological questions can be found elsewhere (2). Below, we only focused on the methods and data necessary to assess the relationship between physical activity and metabolic flexibility. These include the measure of PAL, activity energy expenditure, and descriptions of the training/detraining interventions. A flow chart is presented in the Fig. 1.

The LIPOX study. The LIPOX study was conducted on 10 sedentary and 9 physically active normal-weight male subjects [20 ≤ body mass index (BMI) ≤ 25 kg/m²] and on another group of 9 sedentary overweight subjects (27 ≤ BMI ≤ 35 kg/m²; Table 1). Volunteers were free of any chronic known diseases and were weight stable (±3 kg body wt) for at least 3 mo before enrolment. Normal-weight subjects had no first-degree family history of obesity or type 2 diabetes, while overweight subjects had at least one overweight or diabetic parent. Sedentary or active status was defined using the Monica Optional Study of Physical Activity questionnaire (25), with sedentary subjects reporting sedentary occupations and no structured exercise programs over the 12 mo before enrollment, and active subjects reporting at least 2–3 h/wk of moderate to vigorous leisure physical activity. Additional criteria were the absence of participation to any structured exercise programs over the 12 mo before the study for sedentary subjects, and the involvement in at least one regular sportive activity for active subjects.

Physical inactivity was induced in physically active individuals during 1 mo by stopping all structured physical activities and reducing spontaneous activities of daily living (by taking the elevators, treadmills, using cars, etc.). Training was performed in sedentary normal-weight and overweight subjects, at the level of current recommendations (17) for 2 mo, i.e., four 60-min sessions/wk at 50% peak O₂ uptake (V˙O₂peak) on a cycle ergometer. Throughout the study, research dieticians followed the participants, and the diet was regularly adjusted to maintain subjects in stable energy balance. Informed, written consent was obtained from each subject. The study was approved by the Institutional Review Board of Alsace I (France).

The WISE2005 study. The WISE2005 study was a 2-mo strict bed rest in which 16 healthy normal-weight women (18 ≤ BMI ≤ 25 kg/m²) participated (Table 1). The design and the subjects have been previously fully detailed (3, 5). In brief, the aim was to recruit normally active subjects with a PAL around 1.75, i.e., women who engaged in at least 30 min of moderate activity per day (as structured

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**Fig. 1.** Flow chart of the studies. LIPOX, Strasbourg Lipid Oxidation study; WISE, Women International Space Simulation for Exploration study.
Aerobic exercise was conducted for 40 min in supine positions three times a week, using a specifically designed vertical treadmill. Resistive exercise was performed for 35 min every third day on an elliptical trainer. All exercise protocols were supervised by an exercise physiologist and a medical doctor. Water-derived total body water.

Resting metabolic rate was measured for 1 h using metabolic gas analysis chambers (8). Resting metabolic rate was measured for 1 h using indirect calorimetry (Deltatrac II; GE). PAL was calculated as the ratio of total energy expenditure over resting metabolic rate. Body composition was assessed by hydrodensitometry from the doubly labeled water-derived total body water.

Exercise or as daily-life activities, but did not engage in regular high volume physical activities. After a 20-day baseline ambulatory period, the volunteers were randomly divided into two groups (n = 8 each): one severely detrained group who strictly remained in bed, and one exercise group who performed a high volume combined resistive and aerobic exercise training protocol concomitantly to the bed rest. Restive exercise was performed for 35 min every third day on an inertial flywheel ergometer, allowing subjects to perform maximal concentric and eccentric actions in the supine squat and calf (1). Aerobic exercise was conducted for 40 min in supine positions three to four times per week, using a specifically designed vertical treadmill sequentially graded between 40 and 80% VO2 peak (31).

Energetic and metabolic phenotyping. Before and after the interventions (1 mo of bed rest for the WISE study, 1 mo of detraining and 2 mo of training for the LIPOX study), the participants underwent a series of identical clinical tests. Total energy expenditure was measured using the doubly labeled water method as routinely used in our laboratories (8). Resting metabolic rate was measured for 1 h using indirect calorimetry (Deltatrac II; GE). PAL was calculated as the ratio of total energy expenditure over resting metabolic rate.

Body composition was assessed by hydrodensitometry from the doubly labeled water-derived total body water.

Thirty-six hours before the tests, all subjects were asked to stop any structured physical activities and were provided with microwaveable meals (55% carbohydrate, 15% protein, 30% fat) calculated to match energy requirements. On the test day, subjects were provided with a standard meal including 35% of the daily energy requirements (55% carbohydrate, 15% protein, 32% fat).

Table 1. Characteristics of the participants at baseline and after interventions on physical activity

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>WISE Normally Active Lean Women</th>
<th>LIPOX High Active Lean Men</th>
<th>LIPOX Sedentary Lean Men</th>
<th>LIPOX Sedentary Overweight Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After 1 mo of Bed Rest</td>
<td>After 1 mo of Exercise</td>
<td>Baseline</td>
</tr>
<tr>
<td>n</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Age, yr</td>
<td>33.9 ± 0.8</td>
<td>33.1 ± 0.9</td>
<td>23.6 ± 1.1</td>
<td>27.2 ± 2.9</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>55.6 ± 3.8</td>
<td>52.6 ± 1.4*</td>
<td>58.4 ± 6.5</td>
<td>71.7 ± 2.9a</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>21.3 ± 1.4</td>
<td>19.8 ± 0.4*</td>
<td>21.7 ± 1.4</td>
<td>22.2 ± 0.6*</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>14.8 ± 3.7</td>
<td>14.3 ± 1.3</td>
<td>14.5 ± 3.2</td>
<td>10.5 ± 1.2a</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>26.4 ± 5.5</td>
<td>27.0 ± 1.9</td>
<td>25.0 ± 5.0</td>
<td>14.5 ± 1.4a</td>
</tr>
<tr>
<td>Fat free mass, kg</td>
<td>40.8 ± 3.1</td>
<td>36.1 ± 1.0a</td>
<td>43.8 ± 5.8</td>
<td>61.2 ± 2.5ab</td>
</tr>
<tr>
<td>PAL</td>
<td>1.45 ± 0.28</td>
<td>1.37 ± 0.06*</td>
<td>1.68 ± 0.24</td>
<td>2.23 ± 0.06a</td>
</tr>
<tr>
<td>VO2peak, l/min</td>
<td>1.9 ± 0.4</td>
<td>1.5 ± 0.1*</td>
<td>2.1 ± 0.4</td>
<td>3.6 ± 0.2</td>
</tr>
<tr>
<td>VO2peak, ml·kg⁻¹·min⁻¹</td>
<td>34.5 ± 7.7</td>
<td>28.3 ± 1.9*</td>
<td>35.1 ± 4.4</td>
<td>50.2 ± 2.0a</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects. WISE, Women International Space Simulation for Exploration study; LIPOX, lipid oxidation study; BMI, body mass index; PAL, physical activity level; VO2peak, peak oxygen consumption. *P < 0.05 vs. baseline (paired t-test). a,b,c P < 0.05, values with different superscripted letters are significantly different, whereas values with the same superscripted letters are not. Tukey’s post hoc comparison is following one-way ANOVA within LIPOX groups before physical activity interventions.

Fig. 2. Concept of the variance (Var)-based calculation of metabolic flexibility. NPRQ, nonprotein respiratory quotient; Ins, insulin.

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covering 18% of daily requirements (72% carbohydrate, 18% protein, 11% fat). NPRQ was calculated by using the expired CO$_2$ and the consumed O$_2$ measured hourly and the urinary nitrogen excretion. Blood samples were collected hourly to measure plasma insulin, glucose, and nonesterified fatty acid (NEFA), as previously described (14). Here are reported the results of NPRQ, insulin, glucose, and NEFA over the postprandial period during which data were collected (8 and 10 h for LIPOX and WISE2005 studies, respectively).

**Index of metabolic flexibility.** Overall, metabolic flexibility was assessed with surrogates (close to everyday life), such as response to standardized administration of breakfast and lunch performed before and after the interventions on physical activity of 1) insulin concentration and 2) NPRQ, as assessed by means of indirect calorimetry. The concept we used to assess metabolic flexibility as well as the mathematical approach employed are summarized in Fig. 2.

For each individual, we used the individual insulin and NPRQ kinetics measured hourly over the day test period to calculate the individual variances of the daily NPRQ and insulin responses to the test meals for both the WISE and LIPOX studies and in each condition (before and after the physical activity intervention). As it is mathematically defined, the variance was the sum of the squared distances of each term in the distribution from the mean, divided by the number of terms in the distribution ($N$); $N$ equaled 9 (corresponding to the fasting value and the 8 post-breakfast measurements available over time) for the LIPOX study and 11 (the fasting value and the 10 post-breakfast measurements available) for the WISE study. With such calculations, any potential confounding fasting contribution to the metabolic flexibility index (14) is minimized, and fasting NPRQ contribution becomes similar to that of any other data point collected over the day. The variance-derived indexes assumed a metabolically flexible state when the variance in insulin is low and the variance in NPRQ is high: in other words, when the body has a high capacity to switch from fat to carbohydrate oxidation in association with small changes in insulin concentration in response to feeding. On the opposite, a metabolically inflexible state is assumed when the variance in insulin is high and the variance in NPRQ is low, which is representative of an impaired ability to adapt fuel utilization to fuel availability changes induced by feeding, despite a large amplitude in plasma insulin concentration variations. This definition fits with all description made in the literature, including the original one by Kelly et al. (21, 22).

**Statistical analyses.** To investigate whether insulin and NPRQ variances vary according to changes in the PAL, we categorized all of the subjects’ PAL statuses as “higher PAL” or “lower PAL”. Analyses were done using linear mixed model, taking into account the repeated individual measures according to PAL status (lower PAL vs. higher PAL) and the clustering of subjects in different groups. Random effects were groups and individual within groups. Fixed effect was PAL status. We further adjusted for baseline insulin and fat mass to account for differences in these covariables between the lean and obese groups. The specific effects of training (LIPOX lean sedentary men vs. WISE2005 lean sedentary men).

![Image](http://jap.physiology.org/) Downloaded from http://jap.physiology.org/ by 10.220.33.4 on August 25, 2017

**Fig. 3.** Time course of NPRQ and plasma insulin, glucose, and nonesterified fatty acid (NEFA) concentrations in LIPOX-trained normal-weight men submitted to 1 mo of detraining ($n = 9$), LIPOX sedentary normal-weight men submitted to 2 mo of exercise training ($n = 10$), LIPOX sedentary overweight men submitted to 2 mo of exercise training ($n = 9$), and WISE2005 normally active women ($n = 16$) submitted to bed rest with ($n = 8$) or without ($n = 8$) exercise training. Time 0 corresponds to breakfast ingestion. Time 240 min and 300 min correspond to lunch ingestion in LIPOX and WISE2005 studies, respectively. Values are means ± SE.
the previously published studies on metabolic flexibility during eu-
assessed by simple linear regression. We used a similar approach to were further examined using similar linear mixed model.

and obese subjects) and detraining (LIPOX active subjects and WISE) were further examined using similar linear mixed model.

The relationship between PAL and the variances in NPRQ was assessed by simple linear regression. We used a similar approach to the previously published studies on metabolic flexibility during eu-
glycemic hyperinsulinemic clamps (9), where the variation in NPRQ vs. baseline is expressed as a function of the variation in insulin. Based on that approach, the variance in NPRQ was expressed as a function of the variance in insulin. We then tested the existence of a relationship between the two variances along the ranges of physical activity reached through the combined studies by simple linear regression. We first tested this relationship in healthy lean individuals only because significant between-groups differences in insulin levels were noted with the overweight group. We then added the overweight subjects and reexamined the relationship with all of the subjects when adjusting the analysis on baseline insulin concentrations.

All data are represented as least squares means ± SE, and the level of significance was set as \( P < 0.05 \). All statistics were performed using IBM SPSS version 20.0.

RESULTS

The baseline anthropometric data of the different groups and their responses to the interventions are indicated in Table 1. The kinetics of plasma NEFA, glucose, insulin, and NPRQ in response to the experimental conditions and used in the calculations are indicated in Fig. 3.

When all subjects were classified based on their habitual PAL (lower vs. higher), we showed that interventions on the physical activities, whether aimed to train or detrain individuals, induced the same pattern of responses in terms of metabolic flexibility. Increases in PAL decreased insulin variance \( (P = 0.009) \) and increased NPRQ variance \( (P = 0.002, \text{Fig. } 4) \). We also observed that the variance in NPRQ for all groups was strongly associated with the PAL \( (R^2 = 0.50, P < 0.001, \text{Fig. } 5) \). Such a relationship between PAL and insulin variance was not observed.

To further address how metabolic flexibility was affected by interventions on physical activity, we determined the relationship between daily variances in insulin and NPRQ along the PAL continuum accessible in our groups of subjects. As illustrated in Fig. 6, training/detraining interventions in normal-weight subjects are linearly associated with changes in metabolic flexibility \( (R^2 = 0.65, P = 0.002) \). By adding the overweight sedentary subjects into the relationship and adjusting values on baseline insulin, we observed an even stronger relationship between changes in physical activity and changes in metabolic flexibility \( (R^2 = 0.70, P < 0.001) \).

The specific effects of training and detraining suggest that, although metabolic flexibility responds linearly to PAL, the
impact of detraining was more important than the effect of training, at least in our conditions. Indeed, detraining of normal-weight physically active men and normally active women had opposed effects on daily NPRQ and insulin variances, with a twofold decrease in NPRQ variance ($P = 0.003$) and a concomitantly twofold increase in insulin variance ($P = 0.009$, Fig. 7). Although an improvement was found, the effect of training performed at current recommendation levels in normal-weight and overweight sedentary subjects failed to reach the statistical significance for both daily NPRQ and insulin variances.

**DISCUSSION**

Although a growing body of evidences suggests that metabolic inflexibility is a primary impairment in several metabolic disorders, including obesity, insulin resistance, diabetes, and metabolic syndrome, our knowledge on its causes and on the

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**Fig. 6.** Relationship between variance in insulin and variance in NPRQ. NPRQ and insulin variances are related along the continuum of physical activity in lean subjects only with no adjustment on baseline insulin, as well as in lean and overweight subjects with adjustment on baseline insulin. The sample sizes are indicated in Table 1. Values are means $\pm$ SE.

**Fig. 7.** Longitudinal analysis of the specific effects of training and detraining on daily variances in NPRQ and insulin. $*P < 0.05$, as assessed by a general linear mixed model with time as the repeated measure (before and after training or detraining), subjects and groups as random effects, and baseline insulin and fat mass as covariates. The sample sizes are indicated in Table 1. The effect of the training has been assessed from the following groups: LIPOX lean and overweight men trained for 2 mo according to the current recommendations on physical activity. The effect of detraining has been examined from the following group: WISE active women subjected to bed rest with or without exercise training, and LIPOX lean active men who were asked to stop structured physical activity and reduce spontaneous physical activity. Values are means $\pm$ SE.
way to improve it is still sparse. If the manipulations on the diet and weight loss have been reported to improve metabolic flexibility, the impact of physical activity/exercise per se is surprisingly still missing, as highlighted by Galgani et al. (14). On the contrary, the impact of the adoption of sedentary behaviors, as we can observe it in the general population, on metabolic flexibility received poor attention so far. In this study, we combined cross-sectional and interventional approaches to investigate how habitual PAL, independent of any variations in fat mass, as well as changes in this level, modulate metabolic flexibility.

We showed that both a reduction in spontaneous and structured physical activity and an extreme physical inactivity decreased the variance in daily NPRQ and increased that of insulin. Both of these changes suggest a decreased metabolic flexibility. This statement is consistent with those from previous detraining and bed-rest studies, which reported that a reduction in physical activity induces an increased reliance on carbohydrate as an energy substrate associated with a decrease in fat oxidation, regardless of energy balance conditions (29). The inability to modify fuel oxidation in response to changes in nutrient availability has been implicated in the accumulation of lipid in ectopic tissues and insulin resistance. Interestingly, physical inactivity has been reported to increase fat accumulation in muscle (5) and liver (4), in association with an increase in plasma insulin concentration or a decrease in insulin action (4, 29). Altogether, these data suggest that physical inactivity per se is one of the primary causes in the development of metabolic inflexibility. Some of the mechanisms involved in those metabolic alterations developed in response to physical inactivity have been recently reviewed (4).

Exercise training performed at current recommendations (17) failed to affect metabolic flexibility. Smith et al. (28) in men and Hansen et al. (16) in women reported that an increase in PAL from 1.4 to 1.8 improved fat oxidation adjustment in response to a shift to an eucaloric high-fat diet. Conversely to our studies, the volunteers in Smith’s study were active on the test day, and the measurements of NPRQ in Hansen’s study were calculated over 24 h, including the last session of exercise, whereas our volunteers did not exercise 36 h before the test. The fact that exercise only has a short-term (i.e., ~16 h) beneficial effect on lipid metabolism (26) and insulin sensitivity (24) can explain those differential results.

The intensity, the duration, the rate of the sessions, and/or the duration of our protocol may have been insufficient to impact metabolic flexibility. The observation of an improvement in fasting insulin sensitivity in obese subjects after 7 days of exercise at 70% \( \dot{VO}_2 \text{peak} \), but not at 50% \( \dot{VO}_2 \text{peak} \) as we used it in the LIPOX study, supports this hypothesis (20). Nevertheless, the fact that training following current recommendations affects metabolic flexibility along the linear relationship we observed for habitual baseline PAL supports the idea that exercise does positively affect metabolic flexibility. It is thus possible that current recommendations only tend to, but not significantly, improve metabolic flexibility.

The current recommendations lack of effects may also be simply due to the absence of associated body composition changes, as imposed by the protocol. Indeed, several studies reported that exercise in absence of body mass loss has a relatively modest effect (30) or no effect (12) on insulin sensitivity. Only few studies (13, 19) showed that exercise, without weight loss, increases insulin sensitivity in previously sedentary adults. In fact, we can argue that only one study (19) reported so far a beneficial effect of exercise per se on the response to insulin, since in other study (13) body mass was effectively stable, but body composition changed. We can suggest that the prevention of metabolic inflexibility may be related to the combined effect of exercise and loss of fat mass rather than to the effect of exercise per se.

Overall, the effect of habitual physical activity on metabolic flexibility appears, however, convincing. By looking at the metabolic flexibility combining our different groups as it is classically done, i.e., using the relationship between NPRQ and insulin changes, we again observed that habitual physical activity predicts metabolic flexibility in normal-weight subjects, independent of any overlapping effect of recent exercise and energy balance. Those results support the deleterious effects of sedentariness on metabolic health and give strength to the importance of including physical activity as part of the treatment of metabolic disorders. Our conditions using standard meals expand prior study on metabolic flexibility from acute response from fasting to an infusion to a dynamic

![Fig. 8. Metabolic flexibility represented by variances in NPRQ and insulin in 16 subjects (8 women and 8 men) submitted to 7 days of bed rest from the Blanc at al. (9) study over 5 h after an oral glucose tolerance test. The effect of bed rest on variances in NPRQ and insulin was assessed by using a general linear mixed model with time as the repeated measure (before and after bed rest), and sex and subjects as random effects. Metabolic flexibility decreased after 7 days of bed rest (insulin: \( P = 0.005 \); NPRQ: \( P = 0.002 \)). Values are means ± SE.](image-url)
meal-to-meal response and from responses to supraphysiologically
Glucose/infusion infusions to more clinically relevant
meals. This approach has thus the advantage to mimic free-
living conditions. We, however, acknowledge that one limit of
the present study is the lack of standard measurement of insulin
sensitivity through a euglycemic hyperinsulinemic clamp or an
oral glucose tolerance test. Nevertheless, to confirm our results in
a controlled insulin-stimulated condition, we reanalyzed
data from a 7-day bed-rest study (9) conducted in eight healthy
men and eight healthy women and during which an oral
Glucose Tolerance test was performed before and at the end of
the bed rest. We found lower variances of NPRQ concomi-
tantly to higher variances of insulin during bed rest, supporting
our above observations (Fig. 8). With a sample size of 44,
another limit of our study was limited power to observe small-
to medium-sized effects, such as the exercise training effect in
lean and overweight sedentary men. This is why we essentially
focused our conclusions on the main statistical outcomes. In
doing so, we observed new and original observations linking
habitual physical activity and metabolic flexibility. These main
conclusions are strengthened by the fact that we combined
diverse populations (men vs. women, lean vs. overweight) with
contrasted PAL and complementary phenotyping (objectively
measured cost of activity and metabolic response to standard
meals).

In conclusion, by using an index that accounts for the daily
kinetics of NPRQ and insulin responses to meal ingestion, we
showed that habitual PAL is strongly associated with metabolic
flexibility. Such relationship suggests that an increase in phys-
ical activity on a chronic basis should be associated with an
improvement of metabolic flexibility, whereas a reduction in
PAL should decrease it. A high habitual physical activity is,
therefore, likely to prevent the development of metabolic
diseases characterized by metabolic inflexibility, while the
distribution of sedentary behaviors is likely to enhance their
onset. Future studies will need to determine the PAL threshold
below which metabolic inflexibility is developed to refine the
physical activity recommendations in the general population.

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No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

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