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RESEARCH PAPER

Physical activity and sedentary behavior show distinct associations with tissue-specific insulin sensitivity in adults with overweight

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Abstract

Aim: The aim of this study is to investigate associations between the physical activity (PA) spectrum (sedentary behavior to exercise) and tissue-specific insulin resistance (IR).

Methods: We included 219 participants for analysis (median [IQR]: 61 [55; 67] years, BMI 29.6 [26.9; 32.0] kg/m^2; 60% female) with predominant muscle or liver IR, as determined using a 7-point oral glucose tolerance test (OGTT). PA and sedentary behavior were measured objectively (ActivPAL) across 7 days. Context-specific PA was assessed with the Baecke questionnaire. Multiple linear regression models (adjustments include age, sex, BMI, site, season, retirement, and dietary intake) were used to determine associations between the PA spectrum and hepatic insulin resistance index (HIRI), muscle insulin sensitivity index (MISI) and whole-body IR (HOMA-IR, Matsuda index).

Results: In fully adjusted models, objectively measured total PA (standardized regression coefficient $\beta = 0.17$, $p = 0.020$), light-intensity PA ($\beta = 0.15$, $p = 0.045$) and moderate-to-vigorous intensity PA ($\beta = 0.13$, $p = 0.048$) were independently associated with Matsuda index, but not HOMA-IR ($p > 0.05$). A higher questionnaire-derived sport index and leisure index were associated with significantly lower whole-body IR (Matsuda, HOMA-IR) in men but not in women. Results varied across tissues: more time spent sedentary ($\beta = -0.24$, $p = 0.045$) and a higher leisure index ($\beta = 0.14$, $p = 0.034$) were respectively negatively and positively associated with MISI, but not HIRI. A higher sport index was associated with lower HIRI ($\beta = -0.30$, $p = 0.007$, in men only).

Gijs H. Goossens and Dick H. J. Thijssen Shared last authorship.

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Conclusion: While we confirm a beneficial association between PA and whole-body IR, our findings indicate that associations between the PA spectrum and IR seem distinct depending on the primary site of insulin resistance (muscle or liver).

KEYWORDS
exercise, insulin resistance, sitting, tissue-specific

1 | INTRODUCTION

Obesity and associated impairments in glucose homeostasis are highly prevalent and increase the risk for diabetes type 2 and cardiovascular diseases.[1] It is well established that a lifestyle characterized by high levels of sedentary behavior and low amounts of physical activity (PA) contributes to the development of these chronic diseases.[2] Low levels of PA and more sedentary behavior have repeatedly been associated with insulin resistance (IR) and impaired glucose homeostasis.[3–6] The beneficial effect of exercise training on IR and diabetes prevention is well established.[7]

While IR can develop in several tissues simultaneously, the severity of IR between insulin target tissues can vary between but also within individuals.[8] Consequently, individuals can present with a more prominent muscle or liver IR phenotype.[8,9] It is becoming increasingly accepted that these metabolic phenotypes differ in several important characteristics, including the lipidome, metabolome and inflammatory profiles.[10–12] More specifically, liver insulin resistance has been associated with a more detrimental lipid profile, lower circulating ketone bodies and higher leucine and tyrosine levels compared to muscle insulin resistance.[10,11] On the other hand, muscle IR has been associated with increased systemic inflammation.[12] Considering the direct beneficial effects of PA on skeletal muscle,[13,14] low levels of PA may be more strongly related to development of muscle IR compared to liver IR. Recent studies performed in a controlled laboratory setting have shown that reducing PA and increasing sedentary behavior increases muscle IR, without affecting liver IR in healthy adults,[15] while decreasing sitting time over a period of 4 days improved muscle IR, but not liver IR in overweight and obese women.[16] Moreover, 12 weeks of resistance training selectively improved muscle IR, without affecting liver IR in overweight and obese men.[17] While these findings may suggest that changes in PA specifically alter muscle IR, studies that compare how tissue-specific IR relates to sedentary behavior and physical activity across different intensities are lacking. Therefore, the aim of the present study was to examine the association between the spectrum of PA (from sedentary to moderate-to-vigorous intensity) and tissue-specific IR. We hypothesize that the association between the PA spectrum and muscle IR is stronger than with liver IR. These insights could ultimately guide the development of more personalized interventions for individuals with different IR phenotypes.

2 | RESULTS

Participants ($N = 219$, 60% female) had a median age of 61 [55; 67] years and a median BMI of 29.6 [26.9; 32.0] kg/m^2 (Table 1). The median wear time of the ActivPAL during free-living days was 7 [IQR 6; 8] days. On average, participants were sitting down for 9.3 ± 1.5 h/d and were physically active for 6.4 ± 1.6 h/d (Table 1).

2.1 | Whole-body insulin resistance

The whole spectrum of objectively measured PA (sedentary behavior, total PA, LIPA, MVPA) was associated with Matsuda index in univariate analyses ($p < 0.05$, Table 2), with a positive association for PA outcomes, and a negative association for sedentary behavior. In univariate analysis, total PA and MVPA were negatively associated with HOMA-IR, and sedentary behavior was positively associated with HOMA-IR ($p < 0.05$). In the final model (additional adjustment for PA/sedentary behavior/awake time and diet), all levels of PA (expressed as % of awake time) were significantly associated with Matsuda index (total PA $\beta = 0.17$ [95% CI 0.03–0.31], LIPA $\beta = 0.15$ [95% CI 0.00–0.29], MVPA $\beta = 0.13$ [95% CI 0.00–0.26]), but not with HOMA-IR (Figure 1). There was a significant interaction between sex and the questionnaire-derived sport and leisure index for Matsuda index ($p = 0.009$, $p = 0.002$, respectively) and HOMA-IR ($p = 0.027$, $p = 0.014$, respectively). In men but not women, a higher sport or leisure index was positively associated with Matsuda index (model 4: $\beta = 0.39$ [95% CI 0.20–0.59] and $\beta = 0.39$ [95% CI 0.19–0.59], respectively) and inversely associated with HOMA-IR (model 4: $\beta = -0.26$ [95% CI −0.46–(−0.06)], and $\beta = -0.31$ [95%

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TABLE 1 Participant characteristics

	Total *N* = 219*	Men *N* = 88	Women *N* = 131
Age; years	61 [55; 67]	64 [57; 68]	58 [54; 64]
Sex, female	131 (59.8%)	88 (100.0%)	131 (100.0%)
BMI, kg/m^2	29.6 [26.9; 32.0]	29.2 [27.1; 31.0]	29.8 [26.9; 32.7]
Waist-to-hip-ratio	0.94 (0.09)	1.01 [0.98;1.05]	0.89 [0.84;0.92]
Fat mass, kg	31.9 [27.0; 39.0]	28.0 [24.6; 32.8]	34.8 [30.3; 40.9]
Fat, %	38.4 [31.4; 43.6]	30.3 (4.8)	42.3 (4.5)
Lean mass, kg	50.3 [44.4; 58.4]	61.0 [55.7; 66.7]	45.6 [41.8; 49.0]
Lean, %	58.6 [53.4; 65.2]	66.3 (4.6)	54.8 (4.4)
Android/Gynoid ratio	1.17 [1.06; 1.38]	1.41 [1.27; 1.57]	1.07 [1.01; 1.15]
Use of statins	8 (3.7%)	6 (6.8%)	2 (1.5%)
Use of antihypertensives	31 (14.2%)	14 (15.9%)	17 (13.0%)
Retired	71 (32.4%)	39 (44.3%)	32 (24.4%)
Education level[a]			
Low	12 (5.6%)	6 (6.8%)	6 (4.7%)
Medium	104 (48.4%)	35 (39.8%)	69 (54.3%)
High	99 (46.0%)	47 (53.4%)	52 (40.9%)
Site, WUR	113 (51.6%)	48 (54.5%)	65 (49.6%)
Total energy intake, kcal	2015.1 [1688.3; 2508.8]	2057.5 [1785.0; 2527.6]	1959.1 [1631.6; 2500.0]
Carbohydrates, energy %	41.7 [38.3; 45.5]	41.7 [37.8; 45.7]	41.7 [39.0; 45.3]
Protein, energy %	15.5 [14.2; 17.0]	15.5 [14.2; 17.0]	15.5 [14.3; 17.0]
Fat, energy %	37.4 [34.2; 40.5]	36.4 [33.3; 40.4]	37.6 [34.8; 40.7]
Alcohol, glasses/week	3.0 [0.0; 6.0]	4.0 [2.0; 7.5]	2.0 [0.0; 4.0]
Healthy Diet Index	84.1 (14.6)	81.7 (13.2)	85.8 (15.3)
Sitting, h	9.3 (1.5)	9.8 (1.2)	8.9 (1.5)
Sitting, % awake	59.5 (9.5)	62.8 (7.9)	57.2 (9.9)
Physical activity, h	6.4 (1.6)	5.9 (1.4)	6.7 (1.7)
Physical activity, % awake	40.5 (9.5)	37.2 (7.9)	42.8 (9.9)
LIPA, h	5.1 (1.4)	4.6 (1.3)	5.4 (1.5)
LIPA, % awake	32.7 (8.5)	29.4 (7.0)	34.9 (8.8)
MVPA, h	1.2 [0.9; 1.5]	1.2 [0.9, 1.5]	1.2 [0.9; 1.5]
MVPA, % awake	7.9 (2.6)	7.8 (2.4)	7.9 (2.7)
Leisure index	3.2 [2.8;3.5]	3.2 [2.8; 3.5]	3.2 [3.0; 3.5]
Sport index	2.8 [2.0;3.2]	3.0 [2.0; 3.2]	2.5 [2.2; 3.0]
MISI	0.12 [0.08; 0.19]	0.12 [0.09; 0.18]	0.13 [0.08; 0.20]
HIRI	385.3 [277.9; 554.2]	363.1 [252.3; 497.9]	397.0 [291.2; 569.8]
Matsuda	11.7 [8.3; 16.2]	11.6 [8.7; 14.7]	11.8 [8.3; 18.1]
HOMA-IR	1.8 [1.3;2.3]	1.8 [1.4; 2.3]	1.8 [1.2; 2.3]

Note: Normally distributed data are shown as mean (SD), non-normal data as median [IQR], categorical data as number (%).

Abbreviations: BMI, body mass index; HIRI, hepatic insulin resistance index; LIPA, light-intensity physical activity; MISI, muscle insulin sensitivity index; MVPA, moderate-to-vigorous physical activity; WUR, Wageningen University & Research.

[a]Low: no education, primary education, lower/preparatory vocational education, lower general secondary education, medium: intermediate vocational education, higher general senior secondary education, pre-university secondary education, high: higher vocational education, university.

*For education level: *N* = 215, for dietary information and alcohol consumption: *N* = 214, for leisure/sport index: *N* = 216, for MISI: *N* = 215.

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CI −0.51–(−0.11)], respectively). These sex-specific associations between context-specific PA and whole-body IR were consistent across all models. Excluding participants with studentized residuals >3 did not change our effect estimates substantially (Table S1).

2.2 | Tissue-specific insulin resistance

2.2.1 | Muscle insulin resistance

In univariate models, there were no significant associations between objectively measured PA or sedentary behavior and MISI (Table 3). After adjustment for total PA (model 3), more time spent in sedentary behavior was significantly associated with lower muscle insulin sensitivity (model 3: $\beta = -0.29$ [95% CI −0.53–(−0.05)]). This association remained similar after additional adjustment for diet (model 4: $\beta = -0.26$ [95% CI −0.51–(−0.01)]) and HIRI (model 5: $\beta = -0.24$ [95% CI −0.47–(−0.01)], Figure 2). Moreover, after adjustment for HIRI, there was a trend for positive association between PA% and MISI (model 5: $\beta = 0.13$ (95% CI [−0.00–0.27]) and LIPA% and MISI (model 5: $\beta = 0.14$ [95% CI −0.00–0.28], Figure 1)). Likewise, after adjustment for diet (model 4: $\beta = 0.17$ [95% CI 0.02–0.31]) and HIRI (model 5: $\beta = 0.14$ [95% CI 0.01–0.27]), a higher questionnaire-derived leisure index was associated with higher muscle insulin sensitivity. There were no significant interactions with sex for any of the objective or questionnaire-derived outcomes. Excluding participants with studentized residuals >3 did not change our effect estimates substantially for objective measures of PA (Table S2). Although the direction of the association between the subjective leisure index and MISI remained similar, this was no longer statistically significant (Table S2).

2.2.2 | Hepatic insulin resistance

There was no association between objectively measured PA or sedentary behavior and liver IR in any of the models ($p > 0.05$, Table 3, Figures 1 and 2). There was a significant interaction between sex and the questionnaire-derived sport index for HIRI ($p = 0.025$), but not for any other PA measure (objective or questionnaire-derived). A higher sport index was associated with lower liver IR in men, but not in women (model 5: $\beta = -0.30$ [95% CI −0.52–(−0.08)]). These sex-specific associations between sport index and HIRI were consistent across all models. Excluding participants with studentized residuals >3 did not change our effect estimates substantially (Table S2).

3 | DISCUSSION

Previous studies have convincingly demonstrated that PA has beneficial effects on glucose homeostasis.[3,4,13] The severity of IR can vary between different insulin target tissues such as the liver and skeletal muscle,[8] and physical (in)activity might have distinct effects on tissue-specific insulin sensitivity.[15–17] Here, we show that PA is associated with the Matsuda index, a measure of whole-body IR, thus confirming previous observations. Furthermore, sedentary behavior was associated with muscle IR, but not liver IR, indicating that more sedentary behavior is associated with lower insulin sensitivity in skeletal muscle specifically. Conversely, the questionnaire-derived leisure index was associated with better muscle insulin sensitivity but not liver insulin sensitivity. Finally, higher levels of questionnaire-derived engagement in sport were associated with lower liver IR in men, but not in women. Together, our results show that PA is associated with whole-body IR, yet the associations between PA and tissue-specific IR seem distinct for skeletal muscle and the liver, as illustrated in Figure 3. As we adjusted our models for confounders (including HIRI/MISI for tissue-specific analysis), results are assumed to be independent of these.

PA, including engagement in MVPA, was associated with whole-body IR, a finding that reinforces the known beneficial effect of regular exercise on IR and, ultimately, the risk for developing type 2 diabetes mellitus.[7,13] Beyond this, our study results demonstrate that the relationship between the PA spectrum (from sedentary to MVPA) and IR differs for the liver and skeletal muscle, organs that both play a key role in glucose homeostasis. In line with our hypothesis, we found an inverse association between sedentary time and muscle insulin sensitivity. Previous intervention studies have shown that increasing sedentary times selectively impairs muscle IR,[15] and reducing sedentary behavior selectively improves peripheral (i.e., mainly muscle) insulin sensitivity.[16] Moreover, sedentary behavior has been associated with higher OGTT derived 2 h plasma glucose, which is mainly determined by glucose disposal in skeletal muscle (i.e., muscle IR), but not fasting glucose.[31] Finally, prolonged sitting increases postprandial glucose and insulin levels within hours, compared to regular interruptions with short 2-min bouts of LIPA or MVPA.[32] Taken together, our data provide further evidence for the relation between physical (in)activity and IR and specifically highlight that sedentary behavior is closely linked to muscle IR, but not to liver IR. A potential implication of our findings, together with previous research,[15,16] is that sit-less interventions may be especially beneficial to improve IR in individuals with pronounced IR in skeletal muscle, or combined muscle and liver IR.

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In contrast to sedentary behavior, we found no significant relationship between objectively measured PA and muscle IR, although higher levels of total PA% and LIPA% tended to be associated with higher muscle insulin sensitivity. Moreover, higher leisure PA was significantly associated with higher muscle insulin sensitivity. Lower levels of leisure-time PA have previously been reported in individuals with impaired glucose tolerance, compared to those with impaired fasting glucose[33] and total PA was associated with lower 2 h plasma glucose, but not fasting glucose.[34] Beneficial effects of light-intensity PA on glucose homeostasis are moreover well established.[3] Our results suggest that sedentary behavior, and potentially PA at lower intensities, are specifically associated with muscle IR but not liver IR. However, MVPA was not associated with muscle IR in our study, while previous research shows that exercise has beneficial effects on skeletal muscle insulin sensitivity,[16] which is further supported mechanistically by observations that exercise improves capillarization and increases GLUT4 content in skeletal muscle.[17,35] While objective (MVPA) and subjective (sport index) assessment are in line and do not show an association with muscle IR, inclusion of overweight/obese individuals and exclusion of individuals with MVPA > 4 h/week may have resulted in low variation in MVPA in our study population and therefore reduced the ability to detect associations.

We found no significant association between HIRI and any of the objective measures of PA. However, the subjective sport index was negatively associated with HIRI in men only. It has been suggested that high-intensity training over a longer period of time may be required to improve liver IR, as a moderate-intensity exercise intervention improved liver fat and peripheral/muscle insulin resistance but not liver IR.[36,37] Although the ActivPAL accurately classifies intensity categories (LIPA, MVPA), it does not discriminate between moderate and vigorous PA.[38] These methodological considerations may help to understand the lack of agreement between the ActivPAL-derived MVPA and questionnaire-derived sport index regarding HIRI. Therefore, future studies are needed to better understand the relationship between higher-intensity PA and liver IR. Interestingly, results for HOMA-IR were similar to those for HIRI. In the final models, objectively measured PA was not associated with HOMA-IR or HIRI but the questionnaire-derived sport index was associated with both, in men only. HOMA-IR is often used as an indicator for whole-body IR, but is calculated from fasting glucose and insulin levels, and is therefore closely related to liver IR. This may also explain why results for HOMA-IR and Matsuda index differ in our study. Differences between men and women might be explained by sexual dimorphisms in tissue-specific metabolism.[39] Alternatively, sex differences may relate to the subjective nature of the questionnaire. Indeed, a modified version of the Baecke questionnaire has previously been shown to be more valid for men, compared to women.[40] A bigger range and higher (albeit non-significant) sport index in men compared to women may also contribute to higher discriminative ability in men than women. In summary, our results show that the association between the spectrum of PA and IR is distinct depending on the site of IR (muscle or liver). Interestingly, patterns of association seem opposite for HIRI and MISI (Figure 1), although statistical significance was not always reached.

We examined the PA spectrum in hours and as % of the awake time. Interestingly, for measures of whole-body IR we saw the strongest associations with PA expressed as % of awake time, while sedentary behavior was significantly associated with MISI when expressed as total hours (with a trend for sedentary behavior in hours). Awake times of participants varied greatly in our study (Range: 6.7 h, minimum 11.4 h maximum 18.1 h, median 15.6 [15.1; 16.2] h), which may have contributed to different results for PA h and PA %. Future studies should take note on possible differences in outcomes depending on how the PA spectrum is expressed.

Several strengths and limitations should also be considered alongside the findings of the present study. A strength of this study is the objective assessment of the PA spectrum using accelerometry. Specifically, the ActivPAL is considered as the gold standard to assess sedentary behavior.[41] In addition, PA was assessed during free-living (daily life) conditions rather than standardized laboratory conditions. Furthermore, we investigated the relationship between physical (in)activity and both whole-body and tissue-specific insulin sensitivity, providing unique insight into the relation between physical (in)activity and (tissue-specific) insulin sensitivity. However, this study also has some limitations. First, although the OGTT-derived tissue-specific IR indices (MISI and HIRI) have been validated against the gold standard hyperinsulinemic-euglycemic clamp,[8,19] we did not perform a clamp to assess the relationship between PA and tissue-specific IR in the present study. Second, due to the cross-sectional nature of our study we cannot draw conclusions on causality. Third, although we adjusted the association between PA and IR for known confounders, and results are therefore assumed to be independent of these, we cannot rule out residual confounding. Fourth, due to the explorative nature of this study we did not correct for multiple testing, which can lead to inflation of the type I error rate. Last, accelerometer assessments took place during the first week of a dietary intervention,[18] which might have influenced habitual PA levels. However, if present, we expect that the latter effect would be minor and similar for all study participants and therefore did not significantly impact our conclusions.

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TABLE 2 Association between physical activity and whole-body insulin resistance

			Model 1: Univariate		Model 2: Age, sex, season, site, BMI, pension		Model 3: Age, sex, season, site, BMI, pension, PA/sitting/awake[a]		Model 4: Age, sex, season, site, BMI, pension, PA/sitting/awake[a], diet[b]	
Index	**Activity**		**β [95% CI]**	***p*-value**	**β [95% CI]**	***p*-value**	**β [95% CI]**	***p*-value**	**β [95% CI]**	***p*-value**
Ln Matsuda	Sitting, h		−0.18 [−0.31–(−0.05)]	**0.007**	−0.15 [−0.28–(−0.01)]	**0.033**	−0.06 [−0.29–0.17]	0.592	−0.06 [−0.30–0.18]	0.626
	Sitting, % awake		−0.20 [−0.33–(−0.07)]	**0.003**	−0.16 [−0.30–(−0.03)]	**0.016**	−0.16 [−0.30–(−0.03)]	**0.021**	−0.17 [−0.31–(−0.03)]	**0.020**
	PA, h		0.18 [0.05–0.32]	**0.006**	0.15 [0.02–0.28]	**0.024**	0.10 [−0.12–0.32]	0.362	0.11 [−0.12–0.35]	0.346
	PA, % awake		0.20 [0.07–0.33]	**0.003**	0.16 [0.03–0.30]	**0.016**	0.16 [0.03–0.30]	**0.021**	0.17 [0.03–0.31]	**0.020**
	LIPA, h		0.15 [0.02–0.28]	**0.025**	0.12 [−0.01–0.25]	0.077	0.02 [−0.19–0.23]	0.842	0.06 [−0.16–0.28]	0.602
	LIPA, % awake		0.16 [0.03–0.29]	**0.016**	0.13 [−0.01–0.26]	0.060	0.13 [−0.01–0.27]	0.077	0.15 [0.00–0.29]	**0.045**
	MVPA, h		0.19 [0.06–0.32]	**0.004**	0.16 [0.04–0.29]	**0.010**	0.13 [−0.01–0.27]	0.073	0.08 [−0.06–0.23]	0.267
	MVPA, % awake		0.20 [0.06–0.33]	**0.004**	0.17 [0.04–0.29]	**0.009**	0.17 [0.04–0.29]	**0.010**	0.13 [0.00–0.26]	**0.048**
	Leisure index	Female	0.02 [−0.15–0.20]	0.807	−0.01 [−0.18–0.17]	0.936	−0.03 [−0.21–0.14]	0.733	−0.05 [−0.23–0.14]	0.615
		Male	0.30 [0.09–0.50]	**0.005**	0.35 [0.15–0.54]	**0.001**	0.34 [0.15–0.53]	**0.001**	0.39 [0.19–0.59]	**<0.001**
	Sport index	Female	0.08 [−0.10–0.25]	0.391	0.04 [−0.14–0.22]	0.659	0.02 [−0.16–0.20]	0.827	0.00 [−0.19–0.19]	0.985
		Male	0.32 [0.12–0.53]	**0.002**	0.37 [0.18–0.56]	**<0.001**	0.37 [0.18–0.56]	**<0.001**	0.39 [0.20–0.59]	**<0.001**
Ln HOMA-IR	Sitting, h		0.14 [0.00–0.27]	**0.042**	0.08 [−0.05–0.22]	0.229	−0.02 [−0.25–0.21]	0.878	−0.04 [−0.28–0.20]	0.745
	Sitting, % awake		0.16 [0.03–0.29]	**0.017**	0.11 [−0.02–0.25]	0.095	0.10 [−0.04–0.25]	0.143	0.11 [−0.03–0.25]	0.126
	PA, h		−0.15 [−0.28–(−0.02)]	**0.027**	−0.11 [−0.24–0.02]	0.108	−0.12 [−0.35–0.10]	0.282	−0.15 [−0.39–0.08]	0.199
	PA, % awake		−0.16 [−0.29–(−0.03)]	**0.017**	−0.11 [−0.25–0.02]	0.095	−0.10 [−0.25–0.04]	0.143	−0.11 [−0.25–0.03]	0.126
	LIPA, h		−0.12 [−0.25–0.02]	0.083	−0.08 [−0.21–0.05]	0.239	−0.04 [−0.25–0.17]	0.696	−0.09 [−0.31–0.14]	0.440
	LIPA, % awake		−0.13 [−0.26–0.01]	0.063	−0.08 [−0.22–0.05]	0.230	−0.07 [−0.21–0.07]	0.329	−0.09 [−0.23–0.06]	0.235
	MVPA, h		−0.18 [−0.31–(−0.04)]	**0.009**	−0.14 [−0.26–(−0.01)]	**0.034**	−0.13 [−0.27–0.02]	0.079	−0.10 [−0.25–0.04]	0.170
	MVPA, % awake		−0.18 [−0.31–(−0.05)]	**0.008**	−0.14 [−0.26–(−0.01)]	**0.035**	−0.13 [−0.26–(−0.00)]	**0.042**	−0.11 [−0.24–0.02]	0.097
	Leisure index	Female	−0.04 [−0.22–0.13]	0.628	−0.01 [−0.19–0.17]	0.896	0.00 [−0.18–0.18]	0.996	0.02 [−0.17–0.21]	0.843
		Male	−0.24 [−0.45–(−0.03)]	**0.023**	−0.29 [−0.48–(−0.09)]	**0.004**	−0.28 [−0.48–(−0.09)]	**0.005**	−0.31 [−0.51–(−0.11)]	**0.003**
	Sport index	Female	−0.04 [−0.21–0.14]	0.676	0.00 [−0.18–0.18]	0.972	0.01 [−0.17–0.20]	0.875	0.04 [−0.16–0.23]	0.699
		Male	−0.22 [−0.43–(−0.01)]	**0.038**	−0.24 [−0.44–(−0.04)]	**0.017**	−0.24 [−0.43–(−0.04)]	**0.018**	−0.26 [−0.46–(−0.06)]	**0.013**

Note: Grey background: context-specific measures: Baecke questionnaire. White background: objective measures: ActivPAL. Objective measures: $N = 219$ for models 1–3, $N = 209$ for model 4. Questionnaire outcomes: female: $N = 129$ for models 1–3, $N = 121$ for model 4; male: $N = 87$ for models 1–3, $N = 85$ for model 4. Statistically significant values are highlighted in bold ($p < 0.05$).

Abbreviations: LIPA, light-intensity PA; Ln, natural logarithm; PA, physical activity; MVPA, moderate-to-vigorous PA.

[a]Associations between sedentary behavior and insulin indexes are corrected for physical activity (hours), associations between physical activity and insulin indexes are corrected for sedentary behavior (hours). When expressed as % of awake time, models are corrected for awake time (hours), instead of sedentary time/activity time.

[b]Healthy Diet Index and alcohol consumption.

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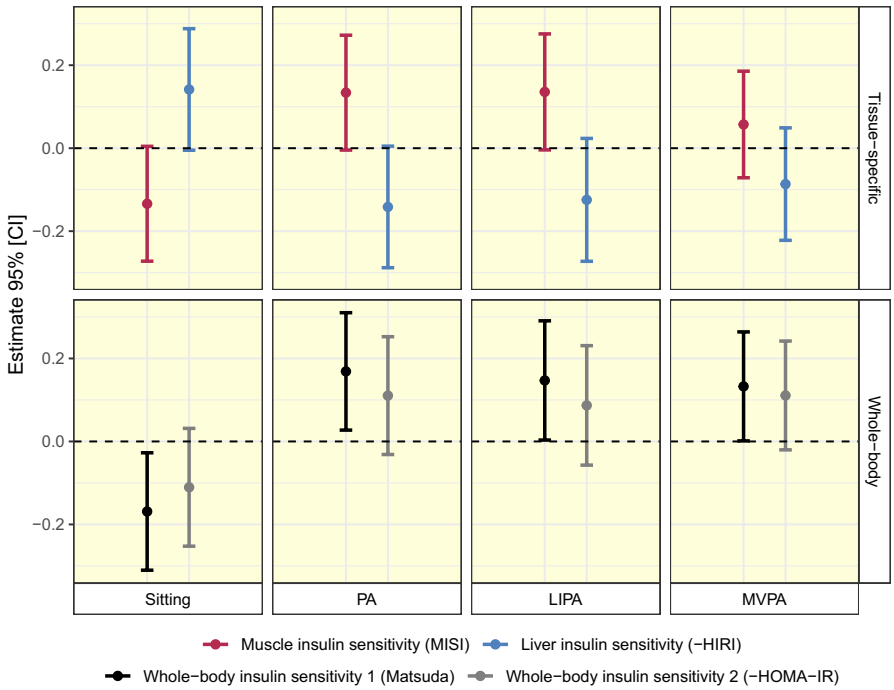

FIGURE 1 Associations between objectively assessed sedentary behavior, physical activity (expressed as % awake time) and insulin sensitivity. Upper panel: tissue-specific insulin resistance, lower panel: whole body-insulin resistance. MISI, muscle insulin sensitivity index; HIRI, hepatic insulin resistance index. HIRI and HOMA-IR were reverse scaled (-HIRI, -HOMA-IR) to ease interpretation as MISI and Matsuda are sensitivity indexes but HIRI and HOMA-IR are resistance indexes. After reverse scaling, higher estimates indicate higher insulin sensitivity for all shown data. (Reverse scaled) standardized estimates with 95% confidence intervals are visualized.

4 | CONCLUSION

We confirm a relationship between PA and whole-body IR. Moreover, we show that sedentary behavior is positively associated with muscle IR but not liver IR and that leisure PA is negatively associated with muscle IR but not liver IR. On the other hand, engagement in sport is inversely associated with liver IR but not muscle IR in men.

These findings indicate that some, but not all, elements of the physical activity spectrum (from sedentary behavior to exercise) show a different association with IR depending on the primary site of IR (muscle versus liver). Further studies are needed to more closely investigate the relationship between sedentary behavior, PA and tissue-specific IR, which may ultimately benefit the development and implementation of more personalized interventions.

5 | MATERIALS AND METHODS

5.1 | Study population

Recruitment of participants (age 40–75 years, body mass index (BMI) 25–40 kg/m^2) took place between 2018 and 2021. Only weight stable (≤3 kg weight gain/loss across a 3-month period) participants with a predominant liver IR or muscle IR phenotype were included, as assessed with a 7-point oral glucose tolerance test (OGTT) and described in detail elsewhere.[18] Individuals with a pre-diagnosis of type 2 diabetes, medications affecting glucose/lipid metabolism and uncontrolled hypertension were excluded. Lifestyle-related exclusion criteria included smoking, alcohol consumption >14 units/week and moderate-to-vigorous PA (MVPA) >4 h/week. A complete list of exclusion criteria is published elsewhere.[18] This resulted in the inclusion of 242 participants, of whom 2 dropped out before assessment of PA. ActivPAL data were not available for 8 participants, due to technical errors (e.g., battery failure). In addition, 13 participants were excluded from the analysis, as ActivPAL measurements included <4 free-living days (1 weekend, 3 weekdays). Resultantly, 219 participants were included for analysis (median age 61, median BMI 29.6 kg/m2, 60% female). Baseline characteristics are shown in Table 1.

5.2 | Study design

This research is part of the PERSonalized glucose Optimization through Nutritional intervention (PERSON)

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TABLE 3 Association between physical activity and tissue-specific insulin resistance

			Model 1: Univariate		Model 2: Age, sex, season, site, BMI, pension		Model 3: Age, sex, season, site, BMI, pension, PA/sitting/awake[a]		Model 4: Age, sex, season, site, BMI, pension, PA/sitting/awake[a], diet[b]		Model 5: Age, sex, season, site, BMI, pension, PA/sitting/awake[a], diet[b], HIRI/MISI	
Index	**Activity**		**β [95% CI]**	***p*-value**	**β [95% CI]**	***p*-value**	**β [95% CI]**	***p*-value**	**β [95% CI]**	***p*-value**	**β [95% CI]**	***p*-value**
Ln MISI	Sitting, h		−0.11 [−0.25–0.02]	0.098	−0.10 [−0.25–0.04]	0.155	−0.29 [−0.53–(−0.05)]	**0.020**	−0.26 [−0.51–(−0.01)]	**0.041**	−0.24 [−0.47–(−0.01)]	**0.045**
	Sitting, % awake		−0.05 [−0.18–0.08]	0.465	−0.03 [−0.18–0.11]	0.652	−0.08 [−0.23–0.07]	0.295	−0.09 [−0.24–0.05]	0.216	−0.13 [−0.27–0.00]	0.058
	PA, h		0.02 [−0.11–0.16]	0.735	0.01 [−0.14–0.15]	0.942	−0.22 [−0.46–0.02]	0.066	−0.17 [−0.42–0.07]	0.167	−0.11 [−0.34–0.12]	0.365
	PA, % awake		0.05 [−0.08–0.18]	0.465	0.03 [−0.11–0.18]	0.652	0.08 [−0.07–0.23]	0.295	0.09 [−0.05–0.24]	0.216	0.13 [−0.00–0.27]	0.058
	LIPA, h		0.01 [−0.12–0.15]	0.845	−0.00 [−0.15–0.14]	0.974	−0.21 [−0.43–0.02]	0.068	−0.15 [−0.38–0.09]	0.222	−0.08 [−0.30–0.14]	0.485
	LIPA, % awake		0.04 [−0.10–0.17]	0.566	0.03 [−0.12–0.17]	0.725	0.07 [−0.08–0.22]	0.344	0.09 [−0.05–0.24]	0.211	0.14 [−0.00–0.28]	0.057
	MVPA, h		0.04 [−0.09–0.18]	0.527	0.03 [−0.11–0.16]	0.711	−0.03 [−0.18–0.13]	0.741	−0.05 [−0.20–0.11]	0.546	−0.04 [−0.19–0.10]	0.536
	MVPA, % awake		0.07 [−0.07–0.20]	0.316	0.05 [−0.09–0.18]	0.470	0.06 [−0.07–0.20]	0.347	0.05 [−0.09–0.18]	0.492	0.06 [−0.07–0.19]	0.381
	Leisure index		0.13 [−0.00–0.27]	0.056	0.13 [−0.00–0.27]	0.055	0.12 [−0.02–0.26]	0.081	0.17 [0.02–0.31]	**0.021**	0.14 [0.01–0.27]	**0.034**
	Sport index		0.11 [−0.02–0.25]	0.099	0.13 [−0.01–0.26]	0.069	0.12 [−0.02–0.26]	0.091	0.14 [0.00–0.28]	0.050	0.07 [−0.06–0.20]	0.297
Ln HIRI	Sitting, h		−0.08 [−0.21–0.06]	0.250	−0.09 [−0.23–0.05]	0.207	0.02 [−0.22–0.26]	0.866	0.01 [−0.24–0.26]	0.934	−0.01 [−0.26–0.23]	0.914
	Sitting, % awake		−0.10 [−0.23–0.04]	0.152	−0.12 [−0.26–0.02]	0.097	−0.11 [−0.25–0.04]	0.150	−0.10 [−0.25–0.05]	0.172	−0.14 [−0.29–0.00]	0.058
	PA, h		0.10 [−0.04–0.23]	0.158	0.12 [−0.02–0.26]	0.090	0.13 [−0.10–0.37]	0.254	0.12 [−0.13–0.36]	0.345	0.14 [−0.10–0.38]	0.265
	PA, % awake		0.10 [−0.04–0.23]	0.152	0.12 [−0.02–0.26]	0.097	0.11 [−0.04–0.25]	0.150	0.10 [−0.05–0.25]	0.172	0.14 [−0.00–0.29]	0.058
	LIPA, h		0.10 [−0.03–0.23]	0.141	0.12 [−0.02–0.26]	0.088	0.13 [−0.09–0.35]	0.252	0.09 [−0.14–0.32]	0.454	0.11 [−0.12–0.34]	0.359
	LIPA, % awake		0.10 [−0.04–0.23]	0.161	0.11 [−0.03–0.25]	0.115	0.10 [−0.05–0.25]	0.178	0.09 [−0.06–0.24]	0.259	0.12 [−0.02–0.27]	0.099
	MVPA, h		0.03 [−0.11–0.16]	0.679	0.05 [−0.08–0.18]	0.462	0.01 [−0.14–0.16]	0.868	0.05 [−0.11–0.20]	0.546	0.05 [−0.10–0.20]	0.526
	MVPA, % awake		0.03 [−0.11–0.16]	0.678	0.05 [−0.09–0.18]	0.501	0.04 [−0.09–0.17]	0.558	0.07 [−0.07–0.21]	0.333	0.09 [−0.05–0.22]	0.210
	Leisure index		0.01 [−0.12–0.15]	0.880	0.01 [−0.12–0.15]	0.873	−0.00 [−0.14–0.13]	0.979	0.01 [−0.13–0.15]	0.911	0.03 [−0.11–0.17]	0.653
	Sport index	Female	0.05 [−0.12–0.23]	0.558	0.06 [−0.12–0.24]	0.504	0.06 [−0.13–0.24]	0.548	0.02 [−0.18–0.22]	0.833	0.02 [−0.18–0.21]	0.874
		Male	−0.30 [−0.50–(−0.09)]	**0.005**	−0.32 [−0.53–(−0.12)]	**0.003**	−0.33 [−0.53–(−0.12)]	**0.002**	−0.32 [−0.53–(−0.10)]	**0.005**	−0.30 [−0.52–(−0.08)]	**0.007**

Note: Grey background: context-specific measures: Baecke questionnaire. White background: objective measures: ActivPAL. Objective measures MISI: $N = 215$ for models 1–3, $N = 205$ for models 4–5. Questionnaire outcomes MISI: $N = 212$ for models 1–3, $N = 202$ for models 4–5. Objective measures HIRI: $N = 219$ for models 1–3, $N = 209$ for model 4, $N = 205$ for model 5. Questionnaire outcomes HIRI: $N = 216$ for models 1–3, $N = 206$ for model 4, $N = 202$ for model 5. Female: $N = 129$ for models 1–3, $N = 121$ for model 4, $N = 120$ for model 5; male: $N = 87$ for models 1–3, $N = 85$ for model 4, $N = 82$ for model 5. Statistically significant values are highlighted in bold ($p < 0.05$).

Abbreviations: HIRI, hepatic insulin resistance index; LIPA, light-intensity PA; Ln, natural logarithm; MISI, muscle insulin sensitivity index; MVPA, moderate-to-vigorous PA; PA, physical activity.

[a]Associations between sedentary behavior and insulin indexes are corrected for physical activity (hours), associations between physical activity and insulin indexes are corrected for sedentary behavior (hours). When expressed as % of awake time, models are corrected for awake time (hours), instead of sedentary time/activity time.

[b]Healthy Diet Index and alcohol consumption.

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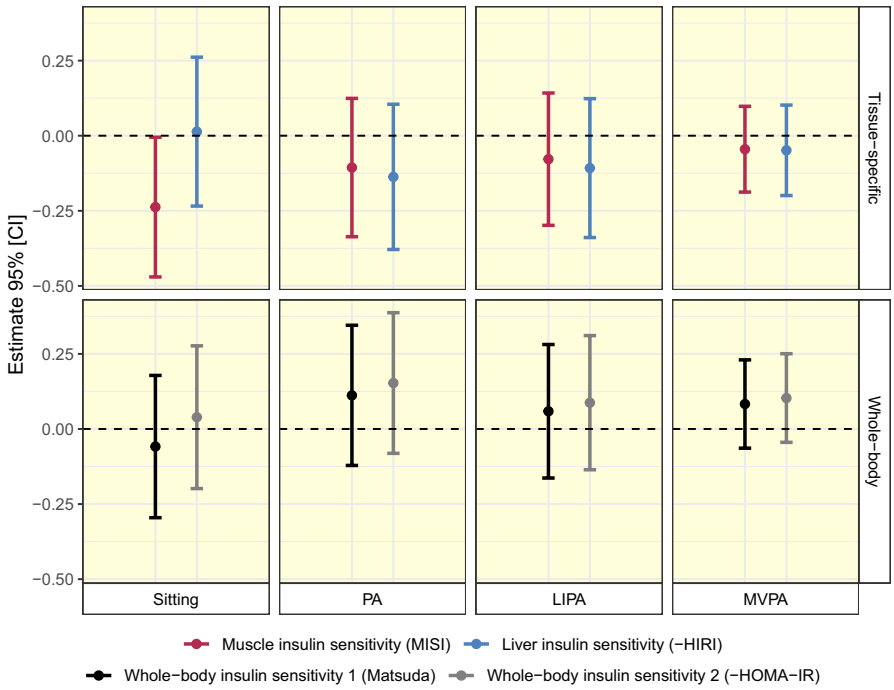

FIGURE 2 Associations between objectively assessed sedentary behavior, physical activity (expressed in hours) and insulin sensitivity. Upper panel: tissue-specific insulin resistance, lower panel: whole body-insulin resistance. MISI, muscle insulin sensitivity index; HIRI, hepatic insulin resistance index. HIRI and HOMA-IR were reverse scaled (-HIRI, -HOMA-IR) to ease interpretation as MISI and Matsuda are sensitivity indexes but HIRI and HOMA-IR are resistance indexes. After reverse scaling, higher estimates indicate higher insulin sensitivity for all shown data. (Reverse scaled) standardized estimates with 95% confidence intervals are visualized.

study.[18] The PERSON study is a two-center, double-blind, controlled dietary intervention study, involving two Dutch centers: Maastricht University Medical Center+ (MUMC+) and Wageningen University & Research. The complete study design is published elsewhere.[18] The PERSON study was approved by the local Medical Ethical Committee (MUMC+; NL63768.068.17), registered at a clinical trial register (ClinicalTrials.gov, NCT03708419) and complied with the Declaration of Helsinki. All participants provided written informed consent before the start of the study.

5.3 | Insulin resistance

Tissue-specific IR was assessed with a 7-point OGTT. The detailed protocol is published in the design paper of the PERSON study.[18] In short, after an overnight fasting blood sample ($t = 0$), participants ingested a 200 mL 75 g glucose drink (Novolab), within 5 min. Blood was drawn again after 15, 30, 45, 60, 90 and 120 min. All blood samples were drawn from an intravenous cannula in the antecubital vein. Plasma glucose and insulin levels were determined in the samples, and the muscle insulin sensitivity index (MISI) and hepatic insulin resistance index (HIRI) were calculated according to Abdul-Ghani et al.[8] The MISI calculation has been optimized by O'Donovan et al.[19] MISI = (dGlucose/dt)/insulin [mean during OGTT in pmol/L], with dGlucose/dt being the rate of decay of plasma glucose concentration (mmol/L) during the OGTT. HIRI = $\text{glucose}_{0\text{-}30}$ [AUC in mmol/L*h] × $\text{insulin}_{0\text{-}30}$ [AUC in pmol/L*h]. In the event of a non-negligible rebound in the glucose curve, the global minimum was used for MISI ($N = 11$). In the event of a peak at 120 min, MISI was not calculated ($N = 4$). Both indexes have been validated against the hyperinsulinemic-euglycemic clamp, the golden standard for assessing (tissue-specific) IR.[8,19] Moreover, the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and Matsuda index were calculated.[20,21] HOMA-IR: fasting glucose (mmol/L)×(fasting insulin (mU/L))/22.5. Matsuda index: 10000 ÷ square root of (fasting plasma glucose (mmol/L) × fasting insulin (pmol/L)) × (mean glucose T0, T30, T60, T90, T120 (mmol/L) × mean insulin T0, T30, T60, T90, T120 (pmol/L)). In case of one missing non-fasting timepoint, Matsuda index was calculated with the remaining 4 timepoints ($N = 4$).

5.4 | Physical activity and sedentary behavior

PA and sedentary behavior were captured with the activPAL3 micro (PAL Technologies Ltd., Glasgow, UK). The

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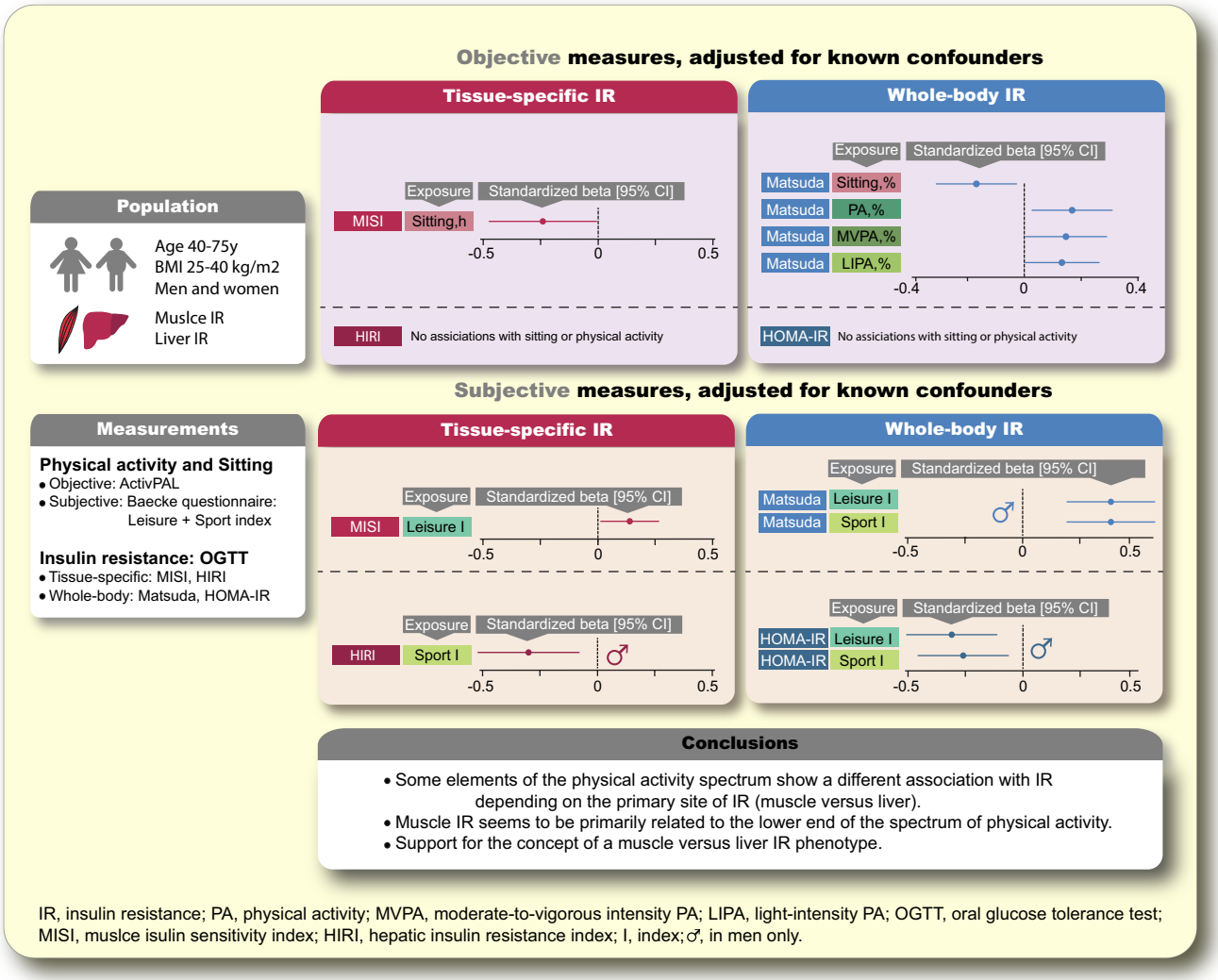

FIGURE 3 Summary of the study design, main results and conclusions.

monitor was waterproofed and attached to the anterior thigh, in the middle between the knee and the greater trochanter. Participants were instructed to maintain their habitual PA/sedentary behavior throughout the measurement period. ActivPAL measurements were done for a consecutive ~14 days. The first ~7 days of activity measurements fell within the assessment week of the PERSON study, where participants visited the research facilities on several days for long hours. As those days are not representative of an individual's habitual physical behavior, they were excluded from analysis. Thereafter, PA assessments continued for ~7 days under 'free-living' conditions. Only free-living days were used to calculate PA/sedentary behavior levels. In case of skin irritations or (battery) failure of the monitor, it was removed sooner. In some cases, participants returned for removal of the monitor after more than 7 days, resulting in more than 7 free-living days being measured. Participants were included for analysis if a minimum of 4 'free-living' days (1 weekend day, 3 week days) was measured.

During the measurement period, participants were asked to keep a sleep/wake diary. ActivPAL data were analyzed with a script from Winkler et al,[22] which was modified to include the sleep/wake data. Sedentary behavior includes waking activities with an energy expenditure ≤1.5 MET, while sitting down or reclining.[23] Light-intensity PA (LIPA) includes standing and stepping times with MET-values <3. MVPA includes activities with MET-values ≥3. PA/sedentary behavior times were calculated as total time (hours) and percentage of the waking time. Moreover, the Baecke questionnaire[24] was used to assess more context-specific PA. This questionnaire allows calculation of an activity index for PA during leisure time and sport.[24] Indexes can take values between 1 and 5, with higher values indicating higher levels of activity. The sport index is based on sport during leisure time. The leisure index is based on

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physical activity, excluding sport (e.g., walking to and from shopping). For TV viewing (sedentary), points are deducted from the leisure index. These indexes thus describe questionnaire-derived PA.

5.5 | Participant characteristics

Participants filled in questionnaires about their education level, retirement status and alcohol use (glasses/week). Habitual dietary intake was assessed with a validated, 163-item food frequency questionnaire.[25] From the FFQ, the Dutch Healthy Diet index 2015 (DHD15) was calculated, which gives an indication of adherence to the Dutch dietary guidelines, on a scale from 0 to 150.[26,27] Adherence is scored from 0 to 10 for the 15 individual components of the Dutch dietary guidelines (e.g., vegetable, fruit, dairy, red/processed meat consumption), resulting in a total score between 0 and 150. The lowest score indicates no adherence, while the highest score indicates complete adherence. Dual-energy X-ray absorptiometry was performed to obtain measures of body composition. Anthropometric measurements included weight, height, hip and waist circumference, which were taken in duplex and averaged. BMI was calculated as weight [kg]/height $[m]^2$.

5.6 | Statistical analysis

Multiple linear regression analysis was used to assess the association between PA/sedentary behavior outcomes and HIRI, MISI, HOMA-IR and Matsuda index. Visual inspection of residual diagnostics revealed deviations from normality, wherefore the IR variables (HIRI, MISI, HOMA-IR, Matsuda) were transformed with the natural logarithm. After transformation, residual analysis revealed no substantial deviations from normality or influential points (Cook's distance). Excluding participants with studentized residuals >3 did not change our results substantially (Tables S1 and S2). Results reported in this manuscript are therefore based on the total group and Ln transformed IR variables. Standardized regression coefficients are reported.

Four models are presented, with the first being univariate, and the second adjusted for age, sex, BMI, season of ActivPAL measurement (spring, summer, fall, winter), site of inclusion (MUMC+, Wageningen University & Research) and retirement status. The third model was additionally adjusted for sedentary behavior (hours) for associations between PA and IR, or adjusted for PA (hours) for associations between sedentary behavior and IR. When activity (sedentary behavior/PA) was expressed as percentage (%) of the awake time, the third model was adjusted for awake time (hours), instead of PA/sedentary behavior. Expression in % takes into account the interconnectedness of physical behavior, meaning that more time spent in PA results in less time spent in sedentary behavior (and vice versa) and therefore does not require additional adjustment for PA/sedentary behavior. The fourth model was additionally adjusted for diet: the DHD15 score (0–150) and alcohol consumption (glasses/week) were both added to the model. As inter-organ crosstalk plays a role in insulin signaling,[28,29] MISI was considered a potential confounder for the association between the spectrum of physical activity and HIRI, and HIRI a potential confounder for the association between the spectrum of physical activity and MISI. Therefore, for tissue-specific outcomes only, a fifth model is presented with results for MISI adjusted for HIRI, and vice versa. This approach was decided on before analysis and is in line with previous research.[10–12]

Effect modification by sex was assessed in the final model (four or five), by addition of an interaction term. Stratified analysis was performed and presented when statistically significant effect modification was present ($p < 0.05$). Where the interaction term was non-significant, results were presented for the whole group. As we found effect modification by sex for some exposure variables, baseline characteristics are also shown for men and women separately. Analyses were performed in R studio, R version 3.6.2.[30] A p-value <0.05 was considered statistically significant.

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CONFLICT OF INTEREST STATEMENT

The authors have declared that no competing interests exist in the writing of this publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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