

How does 6 months of active bike commuting or leisure-time exercise affect insulin sensitivity, cardiorespiratory fitness and intra-abdominal fat? A randomised controlled trial in individuals with overweight and obesity

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/bjsports-2018-100036>).

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Accepted 13 February 2019

ABSTRACT

Objectives To evaluate effects of active bike commuting or leisure-time exercise of two intensities on peripheral insulin sensitivity (primary outcome), cardiorespiratory fitness and intra-abdominal adipose tissue mass (secondary outcomes).

Methods 188 physically inactive, healthy women and men (20–45 years) with overweight or class 1 obesity were recruited. In the 6-month trial, 130 participants were randomised to either: no intervention (CON), active commuting (BIKE) or leisure-time exercise of moderate (MOD, 50% $\text{VO}_{2\text{peak}}$) or vigorous (VIG, 70% $\text{VO}_{2\text{peak}}$) intensity. 100 completed follow-up testing. Exercise prescription was 5 days/week with a weekly exercise energy expenditure of 1600 kcal for women and 2100 kcal for men. Testing was performed at baseline, 3 months and 6 months.

Results Peripheral insulin sensitivity (ml/min/pmol insulin/L) increased (improved) by 24% (95% CI 6% to 46%, $p=0.01$) in VIG compared with CON at 3 months. Peripheral insulin sensitivity increased (improved) by 20% in BIKE (95% CI 1% to 43%, $p=0.04$) and 26% in VIG (95% CI 7% to 47%, $p<0.01$) compared with CON at 6 months. Cardiorespiratory fitness increased in all exercise groups compared with CON at 6 months; but the increase was higher in those that undertook vigorous exercise than those who did moderate exercise. Intra-abdominal adipose tissue mass diminished across all exercise groups in comparison to CON at 6 months.

Conclusions Active bike commuting improved cardiometabolic health; as did leisure-time exercise. Leisure-time exercise of vigorous intensity conferred more rapid effects on peripheral insulin sensitivity as well as additional effects on cardiorespiratory fitness than did moderate intensity exercise.

Trial registration NCT01962259

INTRODUCTION

Physical inactivity and adiposity have reached pandemic proportions and pose major public health concerns, predisposing to cardiovascular diseases, type 2 diabetes and excess mortality.^{1–3} Insulin resistance is a central aetiological factor linking lifestyle to many cardiometabolic disorders,⁴ with additional risk associated with low cardiorespiratory fitness⁵ and increased abdominal obesity.⁶ Exercise

is a remedy for insulin resistance, low fitness and abdominal obesity^{7–9} and plays an important role in the prevention of type 2 diabetes¹⁰ and cardiovascular disease.¹¹

Lack of time has been reported as a major barrier for the engagement in leisure-time exercise.^{12–13} However, physical activity can take place in other domains of everyday life¹⁴ and active commuting represents an alternative means for increasing physical activity.^{15–16} In the recently published global action plan on physical activity for 2018–2030, WHO recommends to strive for increasing active transport,¹⁷ and policy makers are investing to improve bike infrastructure.^{18–19} Still, the current evidence to support beneficial health effects of active commuting by bike is based mainly on observational studies and only a few intervention studies.²⁰ Population-based studies have found active commuting to be associated with lower total and abdominal adiposity, cardiovascular risk and mortality.^{21–25} Likewise, the few randomised^{26,27} and non-randomised^{28–30} intervention studies support beneficial effects of active commuting by bike on cardiorespiratory fitness and cardiovascular risk factors. To date no randomised controlled trials have addressed the effect of active commuting on insulin sensitivity or investigated whether active commuting improves cardiometabolic health similarly to leisure-time exercise.²⁰

Increasing exercise intensity represents another strategy, which can be used to address the lack of time for exercise by reducing the time required to combust a given amount of energy. Moreover, increasing exercise intensity^{17–31–32} rather than dose^{19–33–34} seems to induce additional cardiometabolic health benefits in individuals with overweight and obesity. Still, the impact of exercise intensity on peripheral insulin sensitivity is uncertain.⁸

We designed the study ‘Governing Obesity - Active Commuting To Improve health and Well-being in Everyday life (GO-ACTIWE)’ to evaluate the effects of active commuting by bike compared with leisure-time exercise of moderate and vigorous intensity on peripheral insulin sensitivity as the primary outcome measure and cardiorespiratory fitness and intra-abdominal adipose tissue mass as key secondary outcomes in physically inactive women and men with overweight and class I obesity.



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To cite: Blond MB, Rosenkilde M, Gram AS, et al. *Br J Sports Med* Epub ahead of print: [please include Day Month Year]. doi:10.1136/bjsports-2018-100036

METHODS

Study design

We performed a 6-month single-centre, parallel-group, randomised controlled trial at the Department of Biomedical Sciences, University of Copenhagen, from November 2013 to June 2016 (scheduled date of closure). A comprehensive description of the interdisciplinary study design has been published³⁵ along with data on fat loss,³⁶ low-grade inflammation,³⁷ blood lipids and fibrin turnover.³⁸ We initially planned a 12-month intervention, but on 2 February 2014 the intervention was reduced to 6 months due to recruitment issues and an unexpectedly large withdrawal of eligible individuals during the run-in period. The study adhered to the declaration of Helsinki and written informed consent was obtained from all participants before inclusion.

We recruited healthy Caucasian (self-assigned) physically inactive individuals with overweight and class I obesity (BMI 25–35 kg/m²) aged 20–45 years. Screening included a medical history and the following exclusion criteria were used; body fat <32% for women and <25% for men, peak oxygen uptake (VO_{2peak}) >40 mL O₂/kg/min for women and >45 mL O₂/kg/min for men, fasting plasma glucose >6.1 mmol/L, blood pressure >140/90 mm Hg, abnormal resting or working ECG, parents or siblings diagnosed with type 2 diabetes, habitual medication use (oral contraceptives excluded), and for women, current or planned pregnancy within the time frame of the intervention. Potential participants went through a semistructured interview regarding physical activity habits and were excluded if engaging in structured exercise more than two times/week and/or exceeding 25 km/week of active commuting. The exclusion criteria were chosen to recruit individuals that were physically active less than 1–2 hours per week.

Randomisation and blinding

Participants were randomised by a lottery to one of the following four groups: control (CON), active commuting by bike (BIKE), or moderate (MOD) or vigorous (VIG) intensity leisure-time exercise, in a 1:2:2:2 ratio. The randomisation was stratified by gender and performed in blocks of 7 or 14 participants per strata. Cohabiting couples were offered to be randomised together. The researchers (JSQ, ASG, MBB) accompanying the participants during the lottery were blinded to the ratio of lots in the lottery. The researcher (MRL) who generated the blocks did not partake in the lottery. Neither participants nor researchers were blinded to group allocation after randomisation.

Interventions

The same target exercise energy expenditure was prescribed across all three exercise groups, with women aiming to expend 1600 kcal/week and men 2100 kcal/week. Exercise was prescribed 5 days/week with a prescribed exercise energy expenditure of 320 kcal/day for women and 420 kcal/day for men, equilibrating exercise-induced energy expenditure across genders to ~33 kcal/kg fat-free mass/week.³⁶ The exercise frequency was ramped up during a 3-week period, starting with two exercise days in the first week and incrementing with one exercise day per week until reaching the final frequency of five exercise days per week.

In BIKE, participants were instructed to commute by bike to and from work/school and were, if needed, provided with a bicycle (Nishiki touring master, Nishiki, Denmark) for the duration of the intervention. An average target daily distance was calculated for participants in BIKE based on their energy expenditure while biking; this distance was regularly updated during

the trial to ensure that the achieved energy expenditure corresponded to that prescribed. To achieve the prescribed energy expenditure some participants in BIKE were asked to take a detour on the way to/from work or to use passive transportation for part of their commute. The exercise prescription in MOD and VIG only differed by the prescribed target exercise intensity. Both groups had free access to a chain of fitness centres and participants were instructed to perform aerobic exercise (eg, walking, running, rowing, cross trainer or stationary cycling) at a heart rate corresponding to 50% or 70% of VO_{2peak-reserve},³⁹ respectively.

The target exercise heart rate in MOD and VIG was calculated at baseline based on the heart rate—VO₂ relationship obtained during the graded exercise tests used to assess cardiorespiratory fitness and was updated after 1½ and 3 months. Exercise heart rate (all exercise groups) and distance (BIKE) were monitored using Polar RC3 GPS (Polar, Finland). All training data (heart rate, duration and frequency) were uploaded online (www.polarpersonaltrainer.com) to verify adherence, and participants and investigators were in weekly contact. In case of deviations, participants were asked to increase/decrease daily exercise energy expenditure by 25% until they were within this range again. Participants not achieving a total exercise energy expenditure of 80%–120% of prescription were defined as protocol deviators. Participants in CON were asked to maintain their sedentary lifestyle throughout the study period. Monetary incentives (Danish Kr1000~£120) was provided on completion of an individual intervention segment defined as testing at baseline, 3 months or 6 months, or the intervention itself. If participants did not wish to continue the prescribed intervention they were encouraged to partake in the follow-up testing, especially with regard to the measurement of the primary outcome at 6 months.

Measurements

All outcomes were obtained at baseline and after 3 months and 6 months. Participants were advised to continue habitual eating throughout the study. Each test period comprised three separate test days. Test days 1 and 3 started in the morning (8:00 or 9:00) after an overnight fast (from 22:00 the night before) and test day 2 in the afternoon (15:00 to 18:00) after a 6-hour fast. At all occasions, participants transported themselves by means of car or public transport (bus or train) to the research facilities and avoided excess physical activity. At 3 months and 6 months, we informed participants in the exercise groups to schedule the last exercise bout 36–48 hours before testing to minimise acute effects in order to capture repetitive effects of regular exercise.⁴⁰

Test day 1

Body weight and height were measured (Seca 767, Vogel & Halke, Hamburg, Germany) in light clothing and body composition was determined using dual-energy X-ray absorptiometry (DPX-IQ X-ray bone densitometer 4.7e, Lunar Corporation, Madison, Wisconsin, USA). Brachial blood pressure was recorded thrice after 10 min of rest and an average calculated. Waist circumference was measured at the narrowest point identified between the lowest rib and the iliac crest and an average three measurements calculated. Two sets of arterialised fasting blood samples were drawn to assess fasting plasma glucose and insulin. After this, peripheral insulin sensitivity was determined by a 2-hour one-step hyperinsulinaemic-euglycaemic clamp⁴¹ using previously described procedures.³³ Briefly, hyperinsulinaemia was obtained by a primed continuous infusion of 40 mU/m²/min exogenous human insulin (Actrapid, 100 IU/ml, Novo Nordisk,

Denmark). Plasma glucose was measured frequently and isoglycaemia was maintained by a variable infusion of isotonic glucose. Arterialised blood samples were obtained at 30 min, 60 min, 90 min and 120 min to determine concentrations of glucose and insulin. Peripheral insulin sensitivity was defined as the metabolic clearance rate of glucose from 90 min to 120 min corrected for variations in the glucose concentration in the extracellular distribution space⁴² and divided by steady state plasma insulin concentration. Fasting insulin sensitivity was determined by the approximation formula for the homeostasis model assessment of insulin resistance score (HOMA-IR).⁴³

Test day 2

Cardiorespiratory fitness was determined using an electronically braked cycle (Lode Excalibur, Groningen, Netherlands) and open circuit indirect respiratory calorimetry (Oxycon Pro, Jaeger, Würzburg, Germany). Following a 9-minute warm-up, the workload was increased in a stepwise manner by 20 watts/min and 25 watts/min for women and men, respectively. Attainment of VO_2 peak was accepted when a levelling off in oxygen consumption was observed despite increasing workload or as subjective exhaustion combined with a respiratory exchange ratio >1.15 . Following the exercise test, participants had an intramuscular injection of 20 mg of hyoscinbutylbromid (Buscopan, Sanofi, Denmark) and images of the entire abdomen were obtained by MRI (3 Tesla BiographmMR, Siemens, Germany) using a T1-weighted sequence with water suppression (echo time 9.5 ms, repetition time 685 ms, slice thickness 6 mm, slice spacing 7.2 mm). Participants wore light clothing, lay supine in the scanner and performed breath-holds during image acquisition. Intra-abdominal (visceral and retroperitoneal) adipose tissue volume in the region from the centre of intervertebral disc T10-T11 to the centre of disc L4-L5 was assessed using an automated segmentation procedure⁴⁴ and the volume was converted to mass using an adipose tissue density of 0.92 g/mL.⁴⁵

Test day 3

A mixed meal test was performed in order to access the effects of the interventions on the glucose metabolism under physiological conditions that are closer to that of everyday life. The meal consisted of bread, cheese, jam and a juice with 460 kcal for women and 600 kcal for men with a macronutrient composition of 64 E% carbohydrate, 23 E% fat and 13 E% protein. Blood was sampled for determination of glucose and insulin levels before the meal and every 30 min for 3 hours postprandially. The response to the meal was summarised calculating the area under the curve (AUC) for glucose and insulin using the trapezoid method.

All blood samples were analysed in one batch after completion of the trial by blinded investigators, using absorption photometry (Roche Cobas 8000c702 module) for glucose and electrochemiluminescence immunoassay (Roche Cobas 8000 e602 module) for insulin.

Sample size

The trial was powered to detect changes in peripheral insulin sensitivity (primary outcome), intra-abdominal adipose tissue (secondary outcome) and cardiorespiratory fitness (secondary outcome) following 3 months and 6 months of intervention. All power calculations were based on two-sample t-tests, thereby ignoring the correlation in repeated measurements and were consequently, rather conservative. The α level was 0.05 for all calculations. As the clinically relevant effect size for

peripheral insulin sensitivity measured by the one-step hyperinsulinaemic-euglycaemic clamp is not known, we powered the study based on the efficacy of previous exercise interventions performed by others and ourselves.^{33 46 47} In order to detect a $20 \pm 24\%$ (mean \pm SD) difference in peripheral insulin sensitivity between the exercise groups and CON with a power of 0.85, we would need at least 60 participants (40 in each exercise group and 20 in CON). In order to attain a power of 0.80 for detecting a $16 \pm 24\%$ difference between two exercise groups, we would need to include 74 participants (37 in each exercise group). Similar calculations for cardiorespiratory fitness and intra-abdominal adipose tissue showed that a smaller number of participants was needed.³⁵ With an expected dropout rate of 20% we planned to include 175 participants, but due to a greater than expected rate of withdrawal before and during baseline testing, this was increased to 188 participants.³⁵

Statistical analysis

The statistical analysis of the repeated measures was based on the intention-to-treat principle and included all available data for all randomised participants. For the primary outcome a supplementary analysis including only per protocol completers was performed. All missing data were assumed to be missing at random, or completely at random, in relation to the outcomes. Analyses of repeated measures were performed using baseline constrained mixed linear models with the means as a function of time and group-by-time interaction, thereby ascribing all differences at baseline to the individual level. Gender was included in the model for the analysis of peripheral insulin sensitivity, cardiorespiratory fitness, clamp insulin levels and glucose disposal rate, plus all anthropometric measures, as these outcomes were expected to show a bimodal distribution due to known gender differences. The study was an efficacy study and the intervention effects were estimated by restricted maximum likelihood inference with comparisons of response profiles between groups. An unstructured covariance was used to model the association between the three repeated measurements and denominator degrees of freedom were computed by the method of Kenward and Rogers.⁴⁸ The intervention effects were calculated as response profiles representing the difference between the individual groups at the given follow-up visit with adjustment for covariates and for potential differences at baseline.

Analyses were assessed for adequacy of the assumptions of normality and homogeneity of variances with graphical methods, for the mixed linear models scaled residuals were inspected. Non-Gaussian distributed data (peripheral insulin sensitivity, fasting insulin, HOMA-IR, clamp insulin levels, glucose disposal rate and insulin AUC during the mixed meal) were logarithmically transformed to fit the distributional assumptions of the statistical analyses.

Descriptive data are presented as mean and SD for data with a Gaussian distribution and as median plus the 25th and 75th percentiles IQR for non-Gaussian distributed data. The results from the mixed linear models were expressed as estimated mean differences with 95% CIs for group comparisons and means averaged over covariates (lsmeans) with 95% CIs for levels at a given time point. Comparison of exercise compliance between the three exercise groups was performed using analysis of variance (ANOVA) with post hoc t-tests to compare the individual groups in the case of a significant F-test and likewise non-Gaussian distributed data were analysed using one-way ANOVA on ranks (Kruskal-Wallis H test) and Wilcoxon two-sample test.

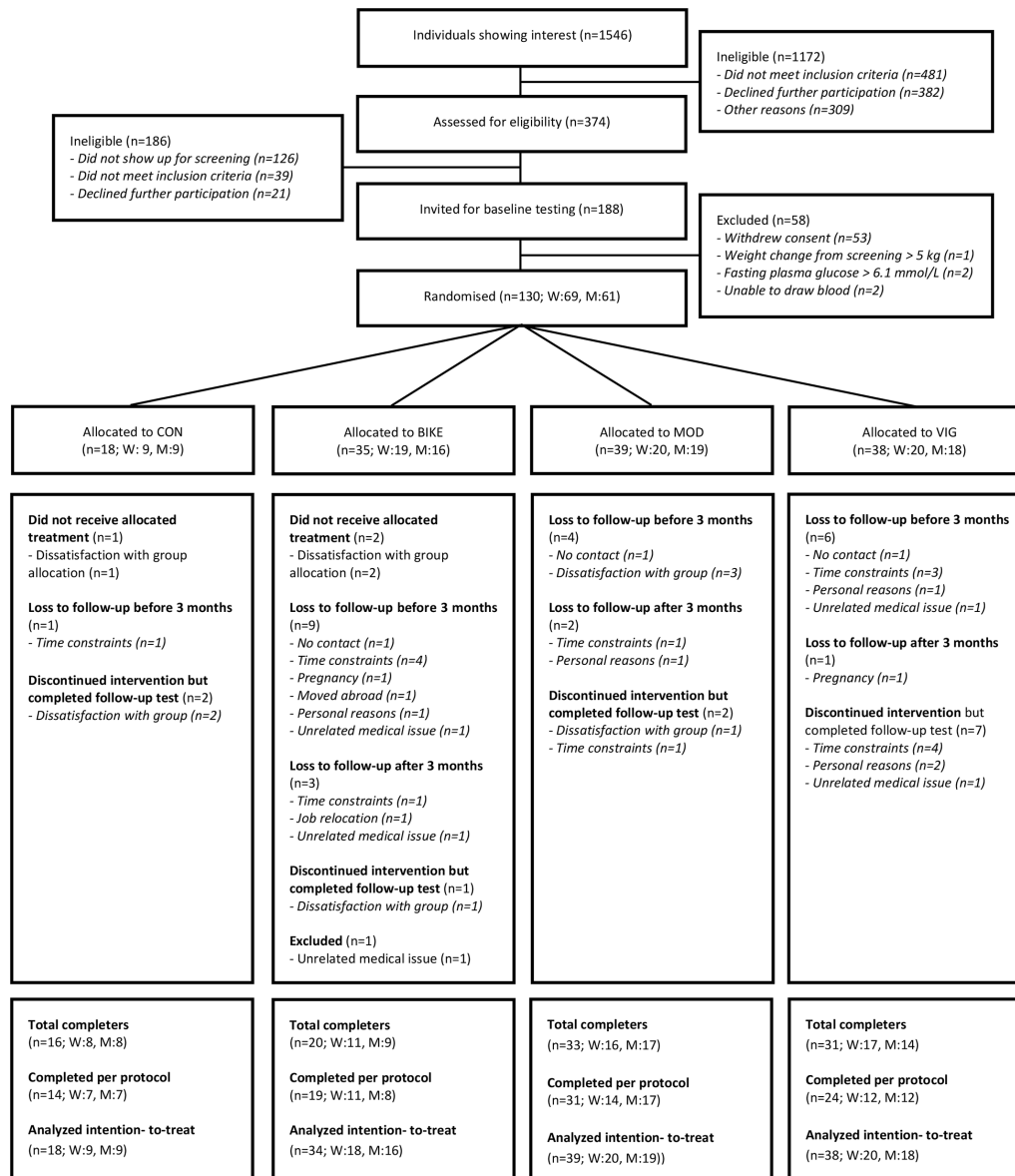


Figure 1 Participant flow chart. BIKE, active commuting group; CON, control group; MOD, moderate intensity exercise group; VIG, vigorous intensity exercise group.

Completers and non-completers were compared at baseline by ANOVA with correction for gender for relevant outcomes.

A value of $p \leq 0.05$ was considered statistically significant. All statistical analyses were performed in SAS V.9.4 (SAS Institute).

Patient involvement

There were no patients involved in defining the research questions or the outcome measured, nor were any patients involved in developing the design of the study. We did not seek patient advice on interpretation or writing of the results.

RESULTS

Participants

The participant flow is presented in figure 1. We included 188 individuals and randomised 130 (women=69; men=61) to CON (n=18), BIKE (n=35), MOD (n=39) and VIG (n=38). One participant (BIKE) was referred for surgery and excluded from further analysis after the discovery of an intra-abdominal

tumour. Baseline participant characteristics are presented in table 1.

Seventy-seven per cent of the participants completed the study; 67% completed the study per protocol. An additional 10% completed measurements of the primary outcome at 6 months, but expended less than 80% of the prescribed total exercise energy expenditure (protocol deviators). Thus, 23% of the participants were missing at 6 months. Six participants (BIKE 3, MOD 2 and VIG 1) attended test days at 3 months but not at 6 months and conversely 12 participants (BIKE 3, MOD 3 and VIG 6) attended the testing at 6 months but not at 3 months. The loss to follow-up at 6 months was 11% for CON, 43% for BIKE, 15% for MOD and 18% for VIG. Non-completers did not differ from completers with respect to peripheral insulin sensitivity (14%, 95% CI -12% to 34%, $p=0.23$), cardiorespiratory fitness ($-0.2 \text{ mL O}_2/\text{kg}/\text{min}$, 95% CI -1.9 to 1.6, $p=0.86$), or intra-abdominal adipose tissue (-111 g , 95% CI -450 to 240, $p=0.51$) (online supplementary table 1).

Table 1 Baseline participant characteristics

	All participants (n=129)	CON (n=18)	BIKE (n=34)	MOD (n=39)	VIG (n=38)
Age, years*	34 (7)	35 (7)	35 (7)	32 (7)	36 (7)
Female, number (%)†	69 (53%)	9 (50%)	19 (54%)	21 (54%)	20 (53%)
Educational level					
Less than college†	67 (52%)	7 (39%)	23 (66%)	21 (53%)	16 (42%)
College†	42 (32%)	5 (28%)	7 (20%)	12 (31%)	18 (48%)
Graduate school†	21 (16%)	6 (33%)	5 (14%)	6 (16%)	4 (10%)
Job status					
Employed, No (%)†	102 (78%)	16 (89%)	28 (80%)	27 (69%)	31 (82%)
Unemployed, No (%)†	11 (8%)	0 (0%)	2 (5%)	5 (13%)	4 (11%)
Student, No (%)†	17 (13%)	2 (11%)	5 (15%)	7 (18%)	3 (7%)
Civil status					
Single, No (%)†	34 (26%)	3 (17%)	8 (23%)	13 (33%)	10 (26%)
Cohabiting, No (%)†	96 (74%)	15 (83%)	27 (77%)	26 (67%)	28 (74%)
Anthropometrics					
Weight, kg*	89.9 (12.5)	91.7 (12.3)	89.6 (11.2)	88.6 (11.6)	90.8 (14.6)
Body mass index, kg/m ² *	29.7 (2.6)	30.1 (2.9)	29.6 (3.2)	29.1 (2.0)	29.8 (2.5)
Fat-free mass, kg‡	53.3 (44.4; 64.9)	52.5 (44.3; 64.1)	54.7 (45.2; 59.7)	52.0 (44.0; 64.9)	51.3 (43.9; 69.0)
Fat mass, kg*	34.7 (7.2)	36.1 (6.3)	34.4 (8.4)	34.3 (7.3)	34.8 (6.4)
Waist circumference, cm*	94 (10)	96 (9)	95 (10)	92 (10)	94 (11)
Intra-abdominal adipose tissue, g‡	1722 (1154; 2703)	2019 (1403; 2514)	1824 (1244; 2629)	1499 (1006; 2253)	1716 (1112; 2866)
Blood pressure					
Systolic, mm Hg*	119 (12)	118 (12)	118 (12)	118 (11)	120 (14)
Diastolic, mm Hg*	76 (9)	77 (11)	77 (11)	75 (7)	77 (8)
Cardiorespiratory fitness					
mL/min*	2628 (601)	2710 (709)	2620 (510)	2590 (580)	2637 (644)
mL/min/kg*	29.0 (5.1)	29.3 (5.9)	29.2 (4.5)	28.8 (5.2)	29.8 (2.4)
Maximal power, watt*	190 (46)	198 (53)	189 (40)	189 (46)	189 (48)
Glucose metabolism					
Fasting glucose, mmol/L*	5.3 (0.4)	5.3 (0.4)	5.3 (0.4)	5.2 (0.4)	5.3 (0.4)
Fasting insulin, pmol/L‡	68.0 (53.4; 94.5)	64.5 (47.6; 115.2)	78.2 (48.6; 110.2)	69.3 (53.6; 96.5)	62.3 (53.5; 75.6)
HOMA-IR‡	2.26 (1.79; 3.09)	2.09 (1.53; 3.96)	2.64 (1.63; 3.69)	2.27 (1.83; 3.08)	2.12 (1.84; 2.65)
Peripheral insulin sensitivity, mL/min/ pmol _{insulin} /L‡	0.66 (0.51; 0.91)	0.69 (0.52; 0.80)	0.63 (0.45; 0.99)	0.66 (0.56; 0.88)	0.70 (0.53; 0.88)
Clamp glucose disposal rate, mg/min‡	309 (242; 448)	303 (240; 389)	298 (240; 424)	357 (235; 448)	305 (264; 473)
Clamp glucose levels, mmol/L*	5.4 (0.5)	5.3 (0.4)	5.4 (0.5)	5.5 (0.6)	5.5 (0.5)
Clamp insulin levels, pmol/L*	520 (108)	503 (139)	512 (115)	535 (110)	518 (82)
AUC glucose mixed meal challenge*	1074 (126)	1116 (142)	1068 (122)	1080 (130)	1055 (120)
AUC insulin mixed meal challenge, 10 ³ ‡	51.3 (37.8; 71.4)	51.3 (42.8; 68.4)	48.5 (34.4; 74.2)	51.4 (37.9; 65.6)	53.1 (34.6; 63.8)

Data are presented as *mean (SD), †number with the percentage of n, or as ‡median (25th centile; 75th centile). Peripheral insulin sensitivity: metabolic clearance rate of glucose measured by the hyperinsulinaemic-euglycaemic clamp.

AUC, area under the curve; BIKE, active commuting group; CON, control group; HOMA-IR, homeostasis assessment of insulin resistance; MOD, moderate intensity exercise group; VIG, vigorous intensity exercise group.

Two participants in BIKE and one in VIG suffered from injuries related to the intervention; all three completed the intervention following a recuperation period, two of them with reduced energy expenditure compared with the prescribed.

Exercise compliance

The compliance with the exercise prescription for participants who attended measurements of the primary outcome at 3 months and 6 months and thereby provided follow-up data for the analyses is presented in table 2. The duration of the exercise intervention, the exercise frequency and the compliance with the number of prescribed exercise days was similar across the three intervention groups. As per study design, the exercise intensity was vigorous in VIG and moderate in MOD. BIKE exercised at moderate intensity. The compliance with the prescribed total exercise energy expenditure was high in all exercise groups

(median 85–101%), but was lower in VIG compared with MOD, in particular, for the 0–6 months period. This was in part due to the fact that we managed to retain more participants in VIG, who did little or no exercise.

Primary outcome analysis

Peripheral insulin sensitivity was improved by 24% in VIG compared with CON at 3 months, whereas BIKE and MOD did not differ from CON (table 3 and figure 2A). At 3 months, peripheral insulin sensitivity in VIG was increased compared with BIKE, but the increase was below the predefined relevant effect size and did not reach statistical significance (15%, 95% CI –0.01 to 33, p=0.06). At 6 months, peripheral insulin sensitivity was increased in VIG (26%) and BIKE (20%) compared with CON, whereas the increase in MOD (17%) was below the prespecified target effect size of 20% and did not reach statistical

Table 2 Exercise compliance for participants in BIKE, MOD and VIG attending measurement of the primary outcome at 3 months and/or 6 months

0–3 months	BIKE (n=20)	MOD (n=32)	VIG (n=26)
Exercise intervention duration, days	93 (86; 107)	97 (85; 106)	92 (89; 102)
Exercise frequency, exercise days/week	4.7 (4.3; 5.1)	5.0 (4.7; 5.3)	5.1 (4.6; 5.3)
Compliance, % of prescribed days	95 (84; 103)	100 (93; 105)	102 (91; 105)
Exercise duration, min/exercise day	46 (39; 54)	52 (46; 61)*	34 (32; 38)*†
Exercise energy expenditure, kcal/exercise day			
Women	331 (268; 348)	342 (303; 377)	300 (271; 334)
Men	448 (427; 493)	455 (395; 515)	410 (307; 474)
Total energy expenditure, % prescribed kcal	101 (88; 110)	100 (92; 118)	97 (77; 104)§
Participants combusting <25% of prescribed kcal			
0–3 months, n	0	0	0
Exercise intensity, %VO ₂ peak reserve	55 (47; 60)	51 (49; 53)	68 (61; 74)††
Exercise intensity, MET	4.9 (4.6; 5.9)	4.9 (4.3; 5.4)	6.4 (5.5; 7.2)††
Heart rate reserve, %	59 (52; 62)	53 (48; 54)	70 (67; 73)††
0–6 months	BIKE (n=20)	MOD (n=33)	VIG (n=31)
Exercise intervention duration, days	190 (181; 198)	188 (182; 196)	188 (183; 198)
Exercise frequency, exercise days/week	4.4 (4.0; 4.9)	4.7 (4.2; 4.9)	4.6 (3.5; 4.9)
Compliance, % of prescribed days	88 (80; 97)	94 (84; 99)	92 (69; 98)
Exercise duration, min/exercise day	42 (38; 53)	54 (48; 60)*	37 (33; 41)*†
Exercise energy expenditure, kcal/exercise day			
Women	322 (315; 355)	322 (294; 371)	300 (275; 322)
Men	473 (426; 501)	471 (384; 504)	428 (370; 499)
Total exercise energy expenditure, % prescribed kcal	94 (90; 99)	91 (86; 109)	85 (65; 97)(†)§
Participants combusting <25% of prescribed kcal			
0–3 months, n	0	1	2
3–6 months, n	1	2	7
0–6 months, n	0	0	6
Exercise intensity, %VO ₂ peak reserve	55 (47; 59)	50 (47; 52)	67 (58; 71)††
Exercise intensity, MET	5.3 (4.6; 6.4)	4.9 (4.3; 5.5)	6.1 (5.0; 7.1)*†
Heart rate reserve, %	59 (53; 62)	52 (49; 56)	68 (64; 72)*†

Data are presented as mean (SD) or median (25th centile; 75th centile).

*P<0.05 compared with BIKE, †p<0.001 compared with BIKE, ‡p<0.001 compared with MOD; §p<0.05 compared with MOD, () indicate p=0.05–0.10.

%VO₂ peak-reserve, percentage of peak oxygen uptake-reserve; BIKE, active commuting group; MET, metabolic equivalent; MOD, moderate intensity exercise group; VIG, vigorous intensity exercise group.

significance ($p=0.053$). Summary of the raw data used for analysis and the number of participants examined at each time point can be found in online supplementary table S2.

The supplementary per protocol analysis for peripheral insulin sensitivity included 88 participants (women=43; men=45) (CON=14; BIKE=19; MOD=31; VIG=24). At 3 months, the peripheral insulin sensitivity in both MOD (19%, 95% CI 1% to 40%, $p=0.03$) and VIG (28%, 95% CI 9% to 52%, $p<0.01$) was increased compared with CON, and the peripheral insulin sensitivity of VIG was higher than in BIKE (18%, 95% CI 1% to 37%, $p=0.04$). At 6 months, peripheral insulin sensitivities in BIKE (27%, 95% CI 6% to 51%), MOD (25%, 95% CI 6% to 47%) and VIG (35%, 95% CI 14% to 51%) were all higher than in CON ($p<0.01$ for all) with no differences between the three exercise groups ($p>0.26$).

Secondary outcome analysis

At 3 months, cardiorespiratory fitness was higher in all exercise groups compared with CON and this effect remained at 6 months (figure 2B, table 3 and online supplementary table S2). Interestingly, cardiorespiratory fitness was higher in BIKE and VIG compared with MOD at 3 months. At 6 months, cardiorespiratory fitness was higher in VIG compared with MOD.

All exercise groups had a lower intra-abdominal adipose tissue mass compared with CON at 3 months and at 6 months;

at 6 months the effect in all exercise groups surpassed the predefined least relevant difference (-215 g) (figure 2C, table 3 and online supplementary table S2). The largest difference observed between the exercise groups was -117 g (95% CI -256 to 23, $p=0.1$) for MOD compared with VIG at 6 months.

Body composition and other metabolic outcomes

Changes in body composition are shown in table 4. All exercise groups exhibited reductions in body weight and fat mass compared with CON. Fat mass was lower in VIG compared with MOD at 6 months. Waist circumference was reduced in both MOD and VIG compared with CON, whereas the reduction in BIKE did not reach statistical significance.

The exercise groups did not differ from CON with regards to fasting plasma glucose or insulin at 3 months, but fasting plasma insulin was decreased in VIG compared with CON after 6 months. Consequently, HOMA-IR was lower in VIG compared with CON (table 4). Fasting plasma insulin and HOMA-IR were also lower in VIG compared with BIKE and MOD at 6 months. Postprandial glycaemic control as determined by total AUC for glucose following a mixed meal challenge was not changed in any of the intervention groups compared with CON (table 4). However, AUC for insulin was decreased in VIG compared with CON at 3 months and 6 months (table 4).

Table 3 Changes in the primary and key secondary outcomes during and after the intervention in the intention-to-treat population

	Estimated mean difference versus CON				P value versus other exercise groups				
	CON (n=18)	BIKE (n=34)	MOD (n=39)	VIG (n=38)					
						BIKE	MOD		
		versus MOD	versus VIG	MOD	versus VIG				
Peripheral insulin sensitivity									
Metabolic clearance rate of glucose, mL/min/pmol _{insulin} /L ^{††}									
3 months	0.68 (95% CI 0.59 to 0.78)	8% (95% CI 9% to 28%)	0.38	0.12	24% (95% CI 6% to 46%)	0.009	0.48	0.06	0.17
6 months	0.66 (95% CI 0.57 to 0.76)	20% (95% CI 11% to 43%)	0.037	0.053	26% (95% CI 7% to 47%)	0.005	0.71	0.56	0.28
Cardiorespiratory fitness									
VO _{2peak} , mL/kg/min*									
3 months	29.3 (95% CI 27.4 to 31.1)	4.4 (95% CI 2.1 to 6.7)	<0.001	0.041	2.2 (95% CI 0.1 to 4.3)	<0.001	0.02	0.71	0.047
6 months	28.5 (95% CI 26.4 to 30.6)	4.9 (95% CI 2.2 to 7.5)	<0.001	0.006	3.4 (95% CI 1.0 to 5.8)	<0.001	0.19	0.44	0.026
Intra-abdominal adipose tissue									
Mass, g*									
3 months	2080 (95% CI 11922 to 2239)	-192 (95% CI 329 to -54)	0.007	0.01	-167 (95% CI 292 to -41)	0.006	0.66	0.99	0.64
6 months	2195 (95% CI 2022 to 2369)	-323 (95% CI 491 to -155)	<0.001	<0.001	-303 (95% CI 456 to -255)	<0.001	0.78	0.21	0.096

Presented results are estimates obtained from the linear mixed models used for the analysis. Data are presented as estimated means (95% CIs) for CON and as estimated mean differences from CON (95% CIs) and p values for BIKE, MOD and VIG. Additionally, p values for comparisons between exercise groups are listed.

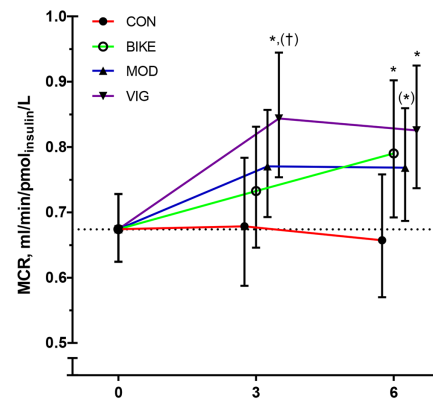
*Adjusted for gender.

†Data were transformed for analysis and results have been back transformed for presentation.

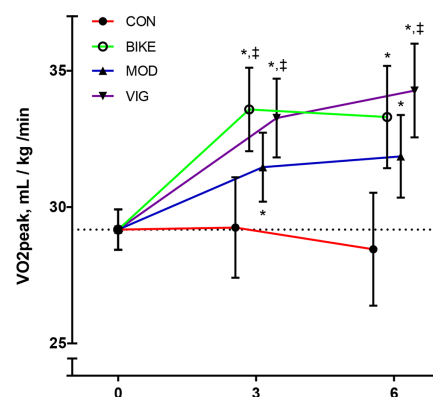
‡Data were transformed for analysis and results have been back transformed for presentation.

BIKE, active commuting group; CON, control group; MOD, moderate intensity exercise group; VIG, vigorous intensity exercise group; VO_{2peak}, peak oxygen uptake.

Peripheral insulin sensitivity



Cardiorespiratory fitness



Intraabdominal adipose tissue

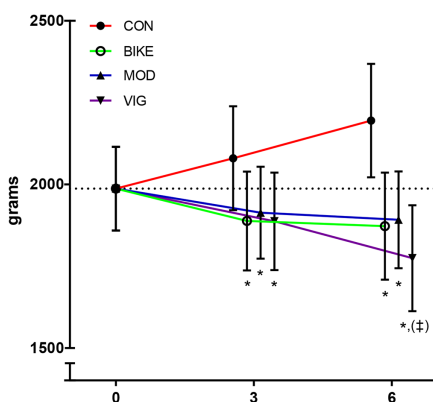


Figure 2 Peripheral insulin sensitivity, cardiorespiratory fitness and intraabdominal adipose tissue mass during the intervention. Effects of active commuting and leisure-time exercise on peripheral insulin sensitivity, cardiorespiratory fitness and intra-abdominal adipose tissue. Depicted values are means, and 95% CIs of the mean, estimated by the mixed linear models used in the analyses. All analyses were corrected for gender. *P<0.05 compared with CON, †p<0.05 compared with BIKE, ‡p<0.05 compared with MOD, (‡) indicate p value 0.05–0.10. BIKE, active commuting group; CON, control group; MCR, metabolic clearance rate of glucose; MOD, moderate intensity exercise group; VIG, vigorous intensity exercise group; VO_{2peak}, peak oxygen uptake.

Discussion

Six months of active commuting by bike led to improvements in peripheral insulin sensitivity and cardiorespiratory fitness on par

Table 4 Changes in descriptive outcomes in the intention-to-treat population

		Estimated mean difference versus CON				P value versus other exercise groups			
		CON (n=18)	BIKE (n=34)	MOD (n=39)	VIG (n=38)	BIKE		MOD	
						versus MOD	versus VIG	versus VIG	versus VIG
Anthropometrics									
Body weight, kg*									
3 months	91.8 (95% CI 89.4 to 94.1)	-2.7 (95% CI -4.8 to -0.6)	0.011	-1.7 (95% CI -3.7 to 0.2)	0.076	0.002	0.27	0.61	0.072
6 months	92.1 (95% CI 89.6 to 94.7)	-3.7 (95% CI -6.2 to -1.3)	0.003	-2.5 (95% CI -4.7 to -0.2)	0.033	<0.001	0.23	0.70	0.074
Fat-free mass, kg*									
3 months	55.9 (95% CI 54.6 to 57.2)	0.9 (95% CI -0.3 to 2.0)	0.15	0.4 (95% CI -0.7 to 1.5)	0.46	0.73	0.35	0.18	0.63
6 months	55.9 (95% CI 54.7 to 57.2)	0.6 (95% CI -0.5 to 1.6)	0.28	0.2 (95% CI -0.8 to 1.2)	0.70	0.44	0.40	0.67	0.64
Fat mass, kg*									
3 months	36.1 (95% CI 34.2 to 37.9)	-3.6 (95% CI -5.5 to -1.8)	<0.001	-2.2 (95% CI -3.9 to -0.5)	0.013	<0.001	0.07	0.86	0.072
6 months	36.3 (95% CI 34.2 to 38.4)	-4.2 (95% CI -6.6 to -1.9)	<0.001	-2.7 (95% CI -4.8 to -0.5)	0.015	<0.001	0.12	0.79	0.041
Waist circumference, cm*									
3 months	95.5 (95% CI 92.7 to 98.2)	-3.1 (95% CI -6.5 to 0.4)	0.080	-3.0 (95% CI -6.1 to 0.1)	0.06	0.009	0.96	0.41	0.31
6 months	95.1 (95% CI 92.6 to 97.6)	-2.9 (95% CI -6.1 to 0.3)	0.076	-4.9 (95% CI -7.8 to -2.0)	0.001	0.001	0.16	0.16	0.96
Glucose metabolism									
Fasting glucose, mmol/L									
3 months	5.3 (95% CI 5.2 to 5.5)	0.0 (95% CI -0.2 to 0.2)	0.75	0.0 (95% CI -0.2 to 0.2)	0.84	0.73	0.88	0.45	0.50
6 months	5.4 (95% CI 5.3 to 5.6)	-0.1 (95% CI -0.3 to 0.1)	0.19	0.0 (95% CI -0.2 to 0.2)	0.85	0.11	0.19	0.86	0.095
Fasting insulin, pmol/L†									
3 months	71 (95% CI 59 to 87)	-11% (95% CI -31% to 14%)	0.36	-2% (95% CI -22% to 23%)	0.86	0.16	0.36	0.63	0.13
6 months	75 (95% CI 62 to 91)	-7% (95% CI -28% to 18%)	0.53	-7% (95% CI -26% to 16%)	0.50	0.002	0.99	0.009	0.003
HOMA-IR†									
3 months	2.4 (95% CI 2 to 3)	-11% (95% CI -31% to 16%)	0.38	-2% (95% CI -23% to 24%)	0.86	0.19	0.39	0.68	0.16
6 months	2.6 (95% CI 2.2 to 3.2)	-11% (95% CI -31% to 16%)	0.40	-9% (95% CI -28% to 16%)	0.45	0.001	0.86	0.013	0.003
Clamp glucose disposal rate, mg/min*†									
3 months	356 (95% CI 314 to 403)	4% (95% CI -1% to 21%)	0.63	10% (95% CI -5% to 27%)	0.19	0.074	0.37	0.15	0.52
6 months	345 (95% CI 303 to 393)	12% (95% CI -5% to 32%)	0.18	12% (95% CI -4% to 30%)	0.16	0.081	0.94	0.77	0.67
Clamp glucose (90–120 min), mmol/L†									
3 months	5.6 (95% CI 5.4 to 5.9)	-0.1 (95% CI -0.4 to 0.1)	0.34	-0.3 (95% CI -0.5 to 0.0)	0.043	0.38	0.26	0.88	0.17
6 months	5.4 (95% CI 5.2 to 5.7)	0.2 (95% CI -0.1 to 0.5)	0.18	0.0 (95% CI -0.2 to 0.3)	0.96	0.81	0.14	0.20	0.83
Clamp insulin (90–120 min), pmol/L*†									
3 months	520 (95% CI 483 to 560)	-2% (95% CI -10% to 8%)	0.70	1% (95% CI -7% to 10%)	0.84	0.12	0.49	0.20	0.028
6 months	539 (95% CI 507 to 574)	-10% (95% CI -16% to -2%)	0.012	-4% (95% CI -11% to 3%)	0.24	0.006	0.086	0.97	0.048
AUC glucose, mixed meal challenge									
3 months	1109 (95% CI 1060 to 1158)	-1 (95% CI -62 to 59)	0.97	-49 (95% CI -105 to 7)	0.083	0.57	0.059	0.56	0.17
6 months	1100 (95% CI 1042 to 1158)	14 (95% CI -61 to 89)	0.71	-34 (95% CI -102 to 35)	0.33	0.22	0.14	0.089	0.71
AUC insulin, mixed meal challenge, 10 ⁴ †									
3 months	54 (95% CI 46 to 63)	-11% (95% CI -26% to 8%)	0.23	-13% (95% CI -27% to 3%)	0.11	0.047	0.72	0.40	0.58
6 months	53 (95% CI 45 to 62)	-11% (95% CI -27% to 8%)	0.23	-10% (95% CI -25% to 7%)	0.23	0.047	0.91	0.42	0.30

Presented results are estimates obtained from the linear mixed models used for the analysis. Data are presented as estimated means (95% CIs) for CON and as estimated mean differences from CON (95% CIs) and p values for BIKE, MOD and VIG. Additionally, p values for comparisons between exercise groups are listed.

*Adjusted for gender.

†Data were transformed for presentation.

AUC, area under the curve; BIKE, active commuting group; CON, control group; HOMA-IR, Homeostasis assessment of insulin resistance; MOD, moderate intensity exercise group; VIG, vigorous intensity exercise group.

with those achieved by vigorous intensity leisure-time exercise. In addition, cardiorespiratory fitness increased in an intensity dependent manner in the leisure-time domain. Intra-abdominal adiposity decreased similarly across all exercise groups.

The GO-ACTIVE trial is the first randomised controlled trial to investigate whether long-term active commuting by bike and leisure-time exercise conveys similar cardiometabolic health benefits. Also, this is the first trial to assess the effect of active commuting by bike on peripheral insulin sensitivity. In addition, the GO-ACTIVE trial is of a substantial magnitude and duration compared with previous randomised controlled trials investigating cardiometabolic effects of active commuting by bike.^{26 27}

Limitations

Nevertheless, a number of limitations need to be addressed. First, for practical reasons the exercise energy expenditure and intensity were not measured directly during the exercise sessions, but estimated from the heart rate during the exercise via the linear relationship between heart rate and oxygen consumption derived from the exercise tests. In addition, the exercise test was performed on a stationary bicycle. There is a concern that this could bias the results for cardiorespiratory fitness by giving BIKE an advantage compared with the other exercise groups, though these groups were encouraged to use a stationary bike as part of their exercise. Furthermore, the study was performed in the greater Copenhagen area, which is highly conducive for commuting by bike. While this is ideal for an efficacy study, our findings cannot be readily generalised to other urban settings. Moreover, some participants in the BIKE group were asked to take a detour or to passively commute part of the way to ensure energy expenditure was in the required range and this detracts from the ecological validity of the study.

Another limitation of the study was the 23% loss to follow-up, which was particularly pronounced in the BIKE and VIG groups. While the retention rate in VIG is comparable to previous randomised trials of similar duration and exercise amount,^{31 32} the level of retention in BIKE was disappointing. Indeed bike is the preferred mode of transportation to and from work/school in the Copenhagen area,⁴⁹ and we speculate that the inclusion of non-habitual bike commuters could in part explain the higher than expected dropout in BIKE. Though we performed the statistical analysis according to an intention-to-treat principle, the missing data made it impossible to conduct a full intention-to-treat analysis. However, the main analysis showed similar results as the per protocol analysis and we regard the results obtained as reliable.

Exercise intensity and insulin sensitivity

The role of exercise intensity for insulin sensitivity is controversial,⁸ potentially owing to differences in methodology and study populations. Larger effects have been suggested for moderate compared with vigorous intensity exercise⁵⁰ and for high compared with low weekly exercise duration.⁵¹ Contrary to this, we found vigorous intensity exercise to convincingly increase peripheral insulin sensitivity, whereas the uncertainty of the effect in MOD did not allow us to confidently claim an effect of moderate intensity exercise on peripheral insulin sensitivity. The findings were obtained in spite of a lower total exercise energy expenditure in VIG compared with MOD. The GO-ACTIVE trial was powered to detect a 20% difference in peripheral insulin sensitivity and with the prior knowledge that exercise increases insulin sensitivity⁸ we believe that lack of statistical power was the reason for not finding a conclusive effect in

What are the findings?

- ▶ 6 months of active commuting by bike provided similar improvements in peripheral insulin sensitivity, cardiorespiratory fitness, and intra-abdominal adiposity as leisure-time exercise for women and men with overweight and obesity.
- ▶ Vigorous intensity leisure-time exercise, but not moderate intensity exercise, improved peripheral insulin sensitivity by 26%.

How might it impact on clinical practice in the future?

- ▶ Healthcare professionals and policy makers can encourage active commuting by bike as an adjunct or alternative to leisure-time exercise for improving cardiometabolic health outcomes in physically inactive women and men with overweight and obesity.

MOD. Importantly, the difference between effects in VIG and MOD was not great enough to claim superiority of VIG.

Our results extend the conclusions of two small randomised controlled trials which reported that only endurance type exercise above moderate intensity improved peripheral insulin sensitivity in elderly participants.^{52 53} The peripheral tissues, the skeletal muscle in particular, are the prime targets for exercise with regards to the glucose metabolism.⁵⁴ Interestingly, the changes in the whole body measures of insulin sensitivity (HOMA-IR and AUC for insulin during the meal test) largely followed the same pattern as the changes in peripheral insulin sensitivity. However, only the VIG group experienced convincing effects, indicating that the improvements in VIG were large enough to elicit effects on the wider glucose metabolism. Thus, our study adds support to the importance of exercise intensity for improving the glucose metabolism.

Exercise and intra-abdominal obesity

Previous studies have shown exercise to be the most efficient lifestyle intervention for reduction of intra-abdominal adipose tissue,⁷ while the effect of exercise intensity on intra-abdominal adipose tissue is still unclear. Quantifying a large proportion of the intra-abdominal adipose tissue, we found a 15–20% decrease in all exercise groups at 6 months. These findings were largely mirrored by the changes in waist circumference.

Exercise intensity and cardiorespiratory fitness

Adding another brick in the wall of the current literature,³¹ we found that improvements in cardiorespiratory fitness increased with exercise intensity. A novel finding is that improvements in cardiorespiratory fitness were similar after active commuting by bike and vigorous intensity leisure-time exercise. Low cardiorespiratory fitness is associated with increased risk of type 2 diabetes, cardiovascular disease and all-cause mortality, and a 10% increase in cardiorespiratory fitness is associated with a 15–20% reduction in fatal cardiovascular disease and possibly an even greater decrease in all-cause mortality.⁵ We recruited participants with low cardiorespiratory fitness and observed increases in cardiorespiratory fitness in excess of 10% in all exercise groups indicating clinical significance of all three interventions.

Healthcare professionals and policy makers can encourage active commuting by bike as an alternative or a supplement

to leisure-time exercise to improve cardiometabolic health in physically inactive women and men with overweight and class II obesity. Future research should focus on how passive commuters can be turned into active commuters and how to consolidate this behaviour.

Contributors MBB, MR, ASG, JSQ and BMS designed and planned the study. MBB, MR, ASG, MT and JSQ performed data collection. MBB, MRLand ANC performed the data analysis. MBB and MR wrote the first draft of the paper and all other authors contributed with intellectual contributions and critical revisions. The final manuscript was read and approved by all authors.

Funding The work is carried out as a part of the research program 'Governing Obesity' funded by the University of Copenhagen's Excellence Programme for Interdisciplinary Research <http://go.ku.dk>. Additional funding was provided by the Faculty of Health and Medical Sciences, University of Copenhagen, TrygFonden (grant number 1081289) and Gerda and Aage Haensch's Fond.

Competing interests The guarantors (MBB, MR and BMS) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethics approval The study was approved by the ethical committee of the Capital Region of Denmark (H-4-2013-108) and registered at the Danish Data Protection Agency.

Provenance and peer review Not commissioned; externally peer reviewed.

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