Physical Activity and Insulin Sensitivity

The RISC Study

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OBJECTIVE—Physical activity is a modifiable risk factor for type 2 diabetes, partly through its action on insulin sensitivity. We report the relation between insulin sensitivity and physical activity measured by accelerometry.

RESEARCH DESIGN AND METHODS—This is a cross-sectional study of 346 men and 455 women, aged 30–60 years, without cardiovascular disease and not treated by drugs for diabetes, hypertension, dyslipidemia, or obesity. Participants were recruited in 18 clinical centers from 13 European countries. Insulin sensitivity was measured by hyperinsulinemic-euglycemic clamp. Physical activity was recorded by accelerometry for a median of 6 days. We studied the relationship of insulin sensitivity with total activity (in counts per minute), percent of time spent sedentary, percent of time in light activity, and activity intensity (whether the participant recorded some vigorous or some moderate activity).

RESULTS—In both men and women, total activity was associated with insulin sensitivity ($P < 0.0001$). Time spent sedentary, in light activity, and activity intensity was also associated with insulin sensitivity ($P < 0.0004/0.01$, 0.002/0.03, and 0.02/0.004, respectively, for men/women) but lost significance once adjusted for total activity. Adjustment for confounders such as adiposity attenuated the relationship with total activity; there were no interactions with confounders. Even in the 25% most sedentary individuals, total activity was significantly associated with better insulin sensitivity ($P < 0.0001$).

CONCLUSIONS—Accumulated daily physical activity is a major determinant of insulin sensitivity. Time spent sedentary, time spent in light-activity, and bouts of moderate or vigorous activity did not impact insulin sensitivity independently of total activity.
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Physical activity is now recognized as a major component of type 2 diabetes prevention; cohort studies have documented the lower risk of incident diabetes even for everyday activities such as walking (1,2). In a post hoc analysis of the Finnish Diabetes Prevention Study, walking for exercise for at least 2.5 h a week in comparison with less than 1 h was associated with a 63–69% lower risk of incident diabetes (3). Physical activity is a complex behavior characterized by intensity, duration, and frequency (4). Various consensus groups recommend physically active lifestyles for adults, with an accumulation of at least 30 min of moderate-intensity aerobic physical activity 5 or more days a week or vigorous-intensity aerobic physical activity for at least 20 min 3 days a week (5). Another important dimension is the time spent in sedentary occupations (6): in the Nurses Health Study, the number of hours spent sedentary was related with incident diabetes even after adjusting for total physical activity (7).

Physical activity may decrease the risk of diabetes by increasing insulin sensitivity (1). Insulin sensitivity has been shown to increase with physical activity, as assessed by questionnaire (8). Objective assessment of physical activity is now possible with unobtrusive accelerometer-based motion sensors (9,10). The aim of this study was to describe the relationship between insulin sensitivity, as measured by the "gold standard" hyperinsulinemic-euglycemic clamp, and habitual physical activity assessed by accelerometer: total activity, activity intensity, and time spent in light and sedentary activities.

RESEARCH DESIGN AND METHODS

In 2002–2004, healthy adults aged 30–60 years without diabetes, hypertension, or dyslipidemia were recruited into the European Relationship between Insulin Sensitivity and Cardiovascular risk (RISC) study (11,12). Each center had ethics committee approval, and participants gave written informed consent.

Participants had a clinical examination and an oral glucose tolerance test and were fitted with an accelerometer, which they returned 1 week later when they presented for a hyperinsulinemic-euglycemic clamp. We report on 346 men and 455 women from 18 clinical centers, with data available on insulin sensitivity and accelerometer-measured physical activity.

Physical activity: accelerometer. Physical activity was measured objectively by a small single-axis accelerometer (Actigraph, AM7164-2.2; Computer Science and Applications, Pensacola, FL) (9,10). The acceleration signal was digitized with 10 samples per second, registered as counts over 1-min intervals. The accelerometer was worn for up to 8 days on a belt in the small of the back, from waking to bedtime except during water-based activities. We analyzed participants with at least 3 days of data, including days when the device was worn more than 10 h; we assumed it was not worn if there were 60 consecutive min with no counts. Accelerometer data were processed with custom software developed for this project using SAS version 9. Data were checked for spurious recording: high counts >20,000 counts/min or repeated counts (13). Our software provided:

- total activity: average number of counts per minute when accelerometer was worn
- activity intensity: any day when accelerometer was worn participants were classified as having *1*) some vigorous activity (>5,724 counts/min for at least 10 consecutive min), *2*) some moderate activity (1,952–5,724 counts/min for at least 10 consecutive min), or *3*) neither moderate nor vigorous activity on any day (9)
- percent time sedentary: <100 counts/min when accelerometer worn (10)
- percent time in light activity: not sedentary nor in moderate or vigorous activity.

Anthropometric measurements. On lightly clad participants, we measured body weight and fat-free mass by bipodal bioelectric impedance (TBF 300; Tanita), height with a stadiometer, and waist circumference with a horizontally placed tailor's tape measure mid-way between the lower costal margin and the iliac crest.

Characteristics. Participants were classified as never smokers, ex-smokers, or current smokers. Family history of diabetes, menopause status, and alcohol intake were obtained from a self-administered questionnaire.

Analytical methods. Local laboratory data were used for study inclusion criteria. Blood collected was stored at −20°C and centrally analyzed in Odense, Denmark, as follows. Plasma glucose was measured by the glucose oxidase technique (Cobas Integra; Roche), and serum insulin was measured by a specific time-resolved fluroimunoassay (AutoDELFIA Insulin kit; Wallac Oy, Turku, Finland).

Insulin sensitivity. We used a 2-h hyperinsulinemic-euglycemic clamp with a primed-continuous infusion rate of 240 pmol/min per m^{-2} and a variable dextrose infusion adjusted every 5–10 min to maintain the plasma glucose level within 0.8 mmol/l (±15%) of target glucose (4.5–5.5 mmol/l). The procedure was standardized across centers using a written protocol and a video demonstration, and data from the clamp were quality controlled centrally (11,12).

Insulin sensitivity is expressed as the ratio of the *M* value averaged over the final 40 min of the clamp and normalized by fat-free mass (FFM) to the mean plasma insulin (*I*) over the final 40 min of the clamp (*M/I*, in $\mu mol \cdot min^{-1} \cdot kg_{FFM}^{-1} \cdot nmol/l^{-1}$) (12).

Statistical analysis. SAS version 9 was used, and statistical significance refers to $P < 0.05$. Logarithms of insulin sensitivity, fasting insulin, and 2-h plasma insulin and average number of counts per minute worn were used in statistical testing. Data are presented transformed to the original units.

Participant characteristics are described by means ± SD or % and compared between sexes by *t* and χ^2 tests. Mixed linear models were used to predict insulin sensitivity adjusted for age class (<40, 40–49, and ≥50 years), for recruitment center as a random factor, and for sex when men and women were combined. Mean insulin sensitivity (95% CI) is shown according to evenly spaced classes of total activity, percent time sedentary, and activity intensity and tested for linear trends. β-Coefficients quantify the relations between insulin sensitivity and activity variables; additional adjustments were made for other activity variables and for potential confounding factors (BMI, waist, fasting glucose, alcohol intake, smoking, diabetes in family, and menopause). The relations between insulin sensitivity and activity variables were linear, as quadratic terms were nonsignificant; interactions with center, age class, and confounders were nonsignificant.

Because sex interactions were nonsignificant, men and women were combined. Total activity and percent time sedentary were divided into quartiles, the mean insulin sensitivity in the resulting 16 categories was estimated, and trend tests were used to compare across quartiles.

TABLE 1
Anthropometric, activity, and metabolic characteristics: the RISC study

	Men	Women	*P*
n	346	455	
Age (years)	43 ± 9	45 ± 8	0.02
<40	42	33	
40–49	33	36	0.02
≥50	25	31	
BMI (kg/m^2)	25.9 ± 3.1	24.4 ± 4.1	0.0001
Waist circumference (cm)	93 ± 10	81 ± 11	0.0001
Smoking (%)			
Current	25	26	
Ex	25	30	0.2
Never	50	44	
Alcohol (g/week)*	102 ± 102	57 ± 67	0.0001
Family history of diabetes (%)	25	27	0.5
Menopause (%)	—	26	—
Accelerometer			
Days worn (*n*)	5.7 ± 1.3	5.7 ± 1.4	0.7
Time worn (h)	89 ± 25	87 ± 25	0.2
Total activity (average counts/min worn)*	374 ± 179	361 ± 156	0.5
Percent time spent			
Sedentary†	62 ± 11	59 ± 11	0.0001
In light activity†	36 ± 11	39 ± 11	0.0001
In moderate or vigorous activity†	2 ± 3	1 ± 2	0.06
Activity intensity group (%)			
Some vigorous activity‡	21	9	
Some moderate activity‡	46	52	0.0001
Neither moderate nor vigorous activity	23	39	
Metabolic parameters			
Insulin sensitivity (*M/I*: $\mu mol \cdot min^{-} \cdot kg_{FFM}^{-1} \cdot nmol/l^{-1}$)*	133 ± 68	161 ± 64	0.0001
Fasting glucose (mmol/l)	5.2 ± 0.5	5.0 ± 0.5	0.0001
2-h glucose (mmol/l)	5.6 ± 1.5	5.8 ± 1.5	0.05
Fasting insulin (pmol/l)*	34.6 ± 17.4	32.4 ± 18.4	0.04
2-h insulin (pmol/l)*	170 ± 159	201 ± 182	0.01

Data are means ± SD unless otherwise indicated. *Logarithm taken for comparing of means. †Vigorous activity, >10 consecutive min with >5,724 counts/min; moderate activity, >10 consecutive min with 1,952–5,724 counts/min; sedentary, <100 counts/min; light activity, neither vigorous or moderate activity nor sedentary. ‡Some vigorous activity, some moderate activity during the period accelerometer was worn.

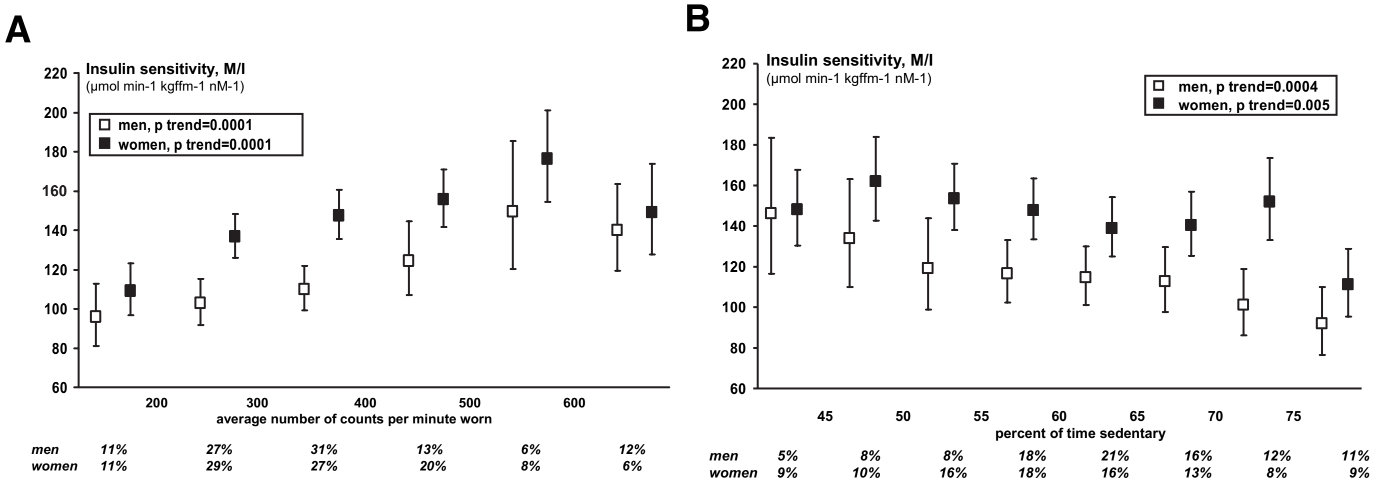
RESULTS

On average, men and women were, respectively, 43 and 45 years of age with BMI of 25.9 and 24.4 kg/m^2 (Table 1). The accelerometers were worn for a median of 6 days, a total of 89 h in men and 87 h in women. While total activity was similar between sexes, men spent more time sedentary and in vigorous- or moderate-intensity activity than women (Table 1). Women spent more time than men in light-intensity activity.

Insulin sensitivity was positively related with total activity, with percent time spent in light activity, and with activity intensity and negatively with time spent sedentary in both men and women (Fig. 1 and Table 2). However, after adjustment for total activity, the relations with insulin sensitivity were no longer significant for other activity variables. Adjustment for other potential confounding factors attenuated the relations between insulin sensitivity and total activity. In the most sedentary quartile group, those with >68% of time sedentary, there was a highly significant relation between insulin sensitivity and total activity (*P* for trend <0.0001) (Fig. 2); for the other quartiles, there was a trend for a positive relation (*P* for trend <0.1, 0.03, and 0.2, respectively). In contrast, for a given quartile group of total activity, there was no significant trend between insulin sensitivity and time spent sedentary (*P* for trend 0.2, 0.4, 0.9, and 0.5, respectively).

DISCUSSION

This is the first study to report the relation between physical activity and insulin sensitivity using the gold



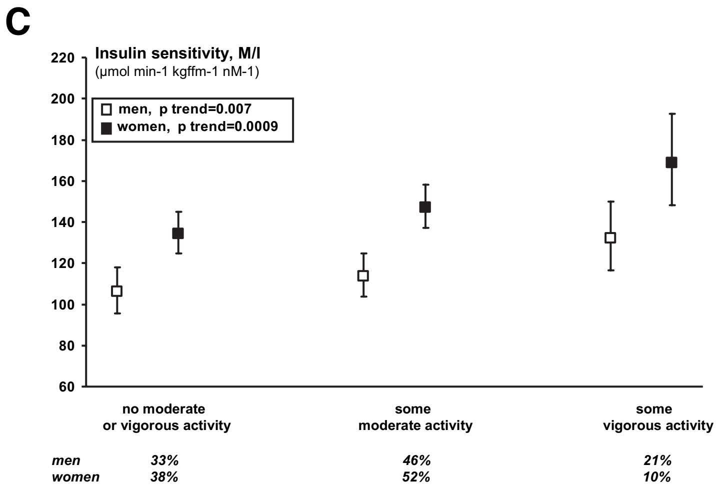


FIG. 1. Mean insulin sensitivity (95% CI) adjusted for age and clinical recruitment center, and characteristics of physical activity measured by accelerometer in men and women according to: mean number of counts/min that the accelerometer was worn (*A*), by percent sedentary time (*B*), and by groups according to some moderate and some vigorous intensity activity (*C*). The RISC study.

standard method for determining insulin sensitivity and an objective measure of activity. Our results show that in both men and women, total physical activity is the key parameter positively related with insulin sensitivity: The percent of time spent sedentary, the percent of time spent in light-activity, and the intensity of activity were not associated with insulin sensitivity after adjusting for total activity. The percent of time spent in moderate or vigorous activity was <2%, with 38% in light activity. Thus, it is the accumulation of physical activity, over the day, that appears to be the determinant of insulin sensitivity. The relation between total activity and insulin sensitivity remained after adjusting for overall (BMI) or abdominal adiposity (waist circumference) or other potential confounders.

In the Insulin Resistance Atherosclerosis Study, insulin sensitivity was quantified by the frequently sampled intravenous glucose tolerance test and physical activity by questionnaires; insulin sensitivity was positively associated with the frequency of vigorous physical activity and also with the energy expended in vigorous and nonvigorous activities (8). Other studies have measured physical activity objectively but used surrogate measures of insulin sensitivity. Total activity as measured by accelerometer has been shown to be more strongly related to fasting insulin than either sedentary or moderately intense activity (10). In line with our results, after 1-year follow-up in the ProActive trial, fasting insulin was significantly associated with change in total body movement, as measured by accelerometer (14). Fasting glucose has been shown to be related to total activity (counts per minutes worn) but not to time spent in sedentary, light-, or moderate- to vigorous-intensity activities (15); in contrast, in the same population, 2-h glucose was related to time spent in all three activities (16).

Among the strengths of the RISC study is the quality control procedure used to evaluate each clamp completed in each clinical center (11). Also, healthy individuals from a wide spectrum of countries were selected for the study; none were receiving drug treatment for diabetes, hypertension, lipids, or obesity, and all had a healthy clinical and biological profile.

We used accelerometer decision rules written specifically for this project, and these rules may affect some of the results (13). We assumed that the accelerometer was not worn if 60 min was recorded with no activity, and consequently we recorded longer percentages of sedentary time than other studies. For moderate or vigorous activity, we required at least 10 min of this type of activity, in line with current physical activity recommendations that refer to “bouts lasting 10 or more min” (5). Activity intensity may be underestimated because it was studied in three groups: more than one-third of the population recorded no moderate or vigorous activity, thus intensity was difficult to study as a continuous variable. Further, it has been reported that the accelerometer underestimates higher-intensity movements (17).

Physical activity can influence insulin sensitivity in many ways, including *1*) enhancing both GLUT4-depen-

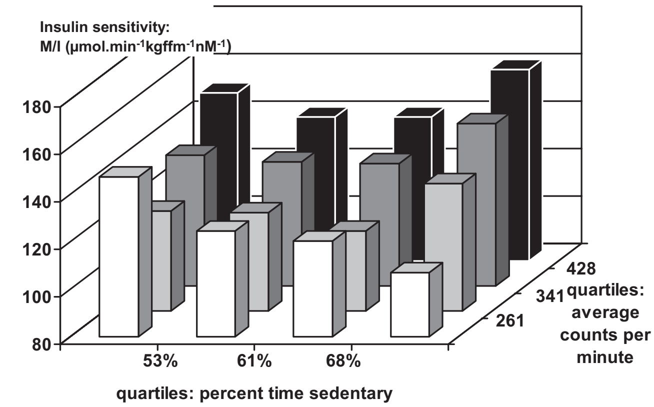
TABLE 2
Relations between activity parameters and insulin sensitivity*: the RISC study

	Men (n = 346)		Women (n = 455)		Men and women (n = 801)	
	β-Coefficient (SE)	P	β-Coefficient (SE)	P	β-Coefficient (SE)	P
Total activity (average number of counts/min worn)* adjusted for:						
Age and center	0.24 (0.06)	0.0001	0.24 (0.05)	0.0001	0.24 (0.04)	0.0001
Age, center, and % time sedentary	0.16 (0.09)	0.06	0.32 (0.07)	0.0001	0.25 (0.05)	0.0001
Age, center, and % time light activity	0.19 (0.07)	0.01	0.29 (0.06)	0.0001	0.24 (0.05)	0.0001
Age, center, and activity intensity (three classes)	0.20 (0.07)	0.006	0.22 (0.05)	0.0001	0.22 (0.04)	0.0001
Age, center, and BMI	0.16 (0.06)	0.0005	0.18 (0.04)	0.0001	0.18 (0.04)	0.0001
Age, center, and waist circumference	0.13 (0.06)	0.02	0.19 (0.04)	0.0001	0.17 (0.04)	0.0001
Age, center, and fasting glucose	0.25 (0.06)	0.0001	0.25 (0.05)	0.0001	0.25 (0.04)	0.0001
Age, center, and alcohol intake*	0.24 (0.06)	0.0001	0.25 (0.04)	0.0001	0.24 (0.04)	0.0001
Age, center, and smoking	0.25 (0.06)	0.0001	0.27 (0.05)	0.0001	0.26 (0.04)	0.0001
Age, center, and diabetes in family	0.24 (0.06)	0.0001	0.24 (0.05)	0.0001	0.24 (0.04)	0.0001
Age, center, and menopause			0.24 (0.05)	0.0001		
% time sedentary, adjusted for:						
Age and center	−0.0096 (0.0027)	0.0004	−0.0049 (0.0019)	0.01	−0.0069 (0.0016)	0.0001
Age, center, and total activity*	−0.0047 (0.0038)	0.2	0.0042 (0.0026)	0.1	0.0005 (0.0022)	0.8
Age, center, and % time light activity	−0.0269 (0.0113)	0.02	−0.0193 (0.0093)	0.04	−0.0213 (0.0071)	0.003
Age, center, and activity intensity (three classes)	−0.0090 (0.0027)	0.0009	−0.0044 (0.0019)	0.02	−0.0064 (0.0016)	0.0001
% time in light activity (% time not sedentary, nor in moderate or vigorous activity), adjusted for:						
Age and center	0.0083 (0.0027)	0.002	0.0043 (0.0019)	0.03	0.0061 (0.0016)	0.0002
Age, center, and total activity*	0.0037 (0.0032)	0.3	−0.0029 (0.0024)	0.2	0.0001 (0.0019)	0.9
Age, center, and % time sedentary	−0.0177 (0.0112)	0.1	−0.0150 (0.0095)	0.1	−0.0149 (0.0072)	0.04
Age, center, and activity intensity (three classes)	0.0088 (0.0027)	0.001	0.0045 (0.0019)	0.02	0.0064 (0.0016)	0.0001
Activity intensity (some moderate vs. neither moderate nor vigorous; some vigorous vs. neither moderate nor vigorous) adjusted for:						
Age and center	0.070 (0.067)		0.091 (0.042)		0.083 (0.036)	
Age, center, and total activity*	0.22 (0.08)	0.02	0.23 (0.07)	0.004	0.22 (0.05)	0.004
	0.017 (0.069)	0.6	0.028 (0.043)	0.4	0.022 (0.038)	0.3
	0.088 (0.092)		0.11 (0.08)		0.085 (0.057)	
Age, center, and % time sedentary	0.055 (0.066)	0.04	0.081 (0.042)	0.006	0.070 (0.036)	0.0004
	0.19 (0.08)		0.22 (0.07)		0.20 (0.05)	
Age, center, and % time light activity	0.064 (0.066)	0.01	0.088 (0.041)	0.003	0.078 (0.036)	0.0001
	0.23 (0.08)		0.24 (0.07)		0.23 (0.05)	

β-Regression coefficients (SEs) adjusted for age class and recruitment center and for sex where men and women combined and then additionally adjusted, one by one, for other activity parameters and potential confounders. *Logarithm of variable.

dent and hypoxia-dependent glucose transport in skeletal muscle (18); *2*) increasing skeletal muscle vascularization, mitochondrial neobiogenesis, and eventually tissue mass (19); *3*) repartitioning intracellular fat, thereby improving its utilization (20); and *4*) fat mass loss. We and others (21,22) have shown that aerobic exercise has a dose- and intensity-related effect to increase insulin signaling and glucose transporter content in skeletal muscle. Exercise training increases insulin-stimulated glucose disposal and GLUT-4 (SLC2A4) protein content in obese patients with type 2 diabetes (22). High levels of sedentary time produce the reverse effect. However, inactivity physiology may be qualitatively different from exercise physiology, with different cellular mechanisms (6). For example, experimental data from animals show that reducing low-intensity activity had a greater effect on skeletal muscle lipoprotein lipase regulation than adding intensive exercise (6). This parallels an Australian study that found that the negative effects on hyperinsulinemia of 14 h per week of television viewing were similar to the beneficial effects of 2.5 h of physical activity (walking and more vigorous activities) (23).

Our study emphasizes that activity has beneficial effects on insulin sensitivity. In this population of men and women aged 30–60 years, total accumulated activity was the important factor rather than intensity of the activity. Even in those who spent most of their time sedentary, more movement during the day from work, household tasks, and commuting, and also from leisure and sporting activities, accumulated to exert a beneficial effect on insulin sensitivity, thus reducing the risk of type 2 diabetes and other diseases associated with insulin resistance. These results highlight the importance of even light activity, which should be taken into account in recommenda-



distribution of participants according to total activity and sedentarity

13%	6%	4%	2%	**>428**	**quartiles:**
8%	**7%**	6%	2%	**341-428**	**average**
3%	9%	**8%**	5%	**261-341**	**counts per**
1%	2%	6%	**16%**	**<261**	**minute worn**
<53%	**53-61%**	**61-68%**	**> 68%**		

quartiles: percent time sedentary

FIG. 2. Mean insulin sensitivity (age, sex, and recruitment center adjusted) and physical activity measured by accelerometer (in men and women combined) by quartiles of average number of counts/min worn and quartiles of percent time sedentary. Table gives the distribution of participants according to total activity and time sedentary quartiles. The RISC study.

tions for increasing the total amount of physical activity in the general population in order to prevent diabetes.

APPENDIX

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Further information on the RISC study and participating centers can be found at www.egir.org.

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