Association between change in daily ambulatory activity and cardiovascular events in people with impaired glucose tolerance (NAVIGATOR trial): a cohort analysis

Thomas Yates, Steven M Haffner, Phillip J Schulte, Laine Thomas, Kim M Huffman, Connie W Bales, Robert M Califf, Rury R Holman, John J V McMurray, M Angelyn Bethel, Jaakko Tuomilehto, Melanie J Davies, William E Kraus

Summary

Background The extent to which change in physical activity can modify the risk of cardiovascular disease in individuals at high cardiovascular risk is uncertain. We investigated whether baseline and change in objectively-assessed ambulatory activity is associated with the risk of a cardiovascular event in individuals at high cardiovascular risk with impaired glucose tolerance.

Methods We assessed prospective data from the NAVIGATOR trial involving 9306 individuals with impaired glucose tolerance who were recruited in 40 countries between January, 2002, and January, 2004. Participants also either had existing cardiovascular disease (if age ≥50 years) or at least one additional cardiovascular risk factor (if age ≥55 years). Participants were followed-up for cardiovascular events (defined as cardiovascular mortality, non-fatal stroke, or myocardial infarction) for 6 years on average and had ambulatory activity assessed by pedometer at baseline and 12 months. Adjusted Cox proportional hazard models quantified the association of baseline and change in ambulatory activity (from baseline to 12 months) with the risk of a subsequent cardiovascular event, after adjustment for each other and potential confounding variables. This study is registered with ClinicalTrials.gov NCT00097786.

Findings During 45 211 person-years follow-up, 531 cardiovascular events occurred. Baseline ambulatory activity (hazard ratio [HR] per 2000 steps per day 0·90, 95% CI 0·84–0·96) and change in ambulatory activity (0·92, 0·86–0·99) were inversely associated with the risk of a cardiovascular event. Results for change in ambulatory activity were unaffected when also adjusted for changes in body-mass index and other potential confounding variables at 12 months.

Interpretation In individuals at high cardiovascular risk with impaired glucose tolerance, both baseline levels of daily ambulatory activity and change in ambulatory activity display a graded inverse association with the subsequent risk of a cardiovascular event.

Funding Novartis Pharmaceuticals.

Lancet 2014; 383: 1059–66

Published Online December 20, 2013 http://dx.doi.org/10.1016/S0140-6736(13)62061-9

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NIHR Leicester-Loughborough Diet, Lifestyle, and Physical Activity Biomedical Research Unit, Leicester, UK (T Yates PhD, M J Davies MD); **Leicester Diabetes Centre, College of Medicine, Biological Sciences and Psychology, University of Leicester, Leicester, UK** (T Yates, M J Davies); **Shavano Park, USA** (S M Haffner MD); **Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, USA** (P J Schulte PhD, L Thomas PhD, K M Huffman MD, C W Bales PhD, R M Califf MD, W E Kraus MD); **Durham VA Medical Center, Durham, NC, USA** (C W Bales); **Diabetes Trials Unit, University of Oxford, Oxford, UK** (M A Bethel, MD, R R Holman MD); **British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK** (J J V McMurray MD); **Centre for Vascular Prevention, Danube University Krems, Krems, Austria** (J Tuomilehto MD); **South Ostrobothnia Central Hospital, Seinajoki, Finland** (J Tuomilehto); **and King Abdulaziz University, Jeddah, Saudi Arabia** (J Tuomilehto)

Correspondence to Dr Thomas Yates, Leicester Diabetes Centre, Leicester General Hospital, Leicester LE5 4PW, UK **ty20@le.ac.uk**

Introduction

Clinical trials have shown that lifestyle interventions can effectively reduce the risk of developing type 2 diabetes in high-risk individuals with impaired glucose tolerance,[1,2] and detailed modelling analyses have shown them to be highly cost-effective in the prevention of type 2 diabetes.[3,4] Consequently, lifestyle changes form the cornerstone of diabetes prevention initiatives that have been translated into routine clinical practice.[5,6] However, whether changes to lifestyle factors affect the risk of cardiovascular disease in individuals with impaired glucose tolerance is unclear, since previous diabetes prevention trials were not designed, and consequently lack sufficient power, to assess this outcome. This is an important limitation, since cardiovascular disease is the most deleterious consequence of dysglycaemia and the primary cause of death in those with type 2 diabetes.[7]

Observational studies have consistently shown that higher levels of physical activity or cardiorespiratory fitness are associated with a lower risk of cardiovascular morbidity and mortality.[8–11] However, this evidence has been limited by several factors. Physical activity is usually assessed by self-reported questionnaires, which are known to have poor validity, particularly when assessing habitual or total physical activity levels.[12] Alternatively, cardiorespiratory fitness, even when measured objectively, is affected by factors beyond physical activity, including genetic makeup, which also affect survival.[13] Along with limitations around measurement, the extent to which change in physical activity can act to ameliorate the risk of cardiovascular disease in individuals already displaying impaired glucose tolerance and other cardiovascular risk factors is also unknown.

The NAVIGATOR trial provides the first detailed opportunity in an international pharmacotherapy trial to investigate whether change in objectively-assessed ambulatory activity is associated with a lower risk of a cardiovascular event independently of randomised therapy allocation, other lifestyle factors, or body-mass index.

Methods

Study design and population

We analysed prospective data from NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research),[14–16] a multicentre, randomised, placebo controlled, 2×2 factorial trial designed to investigate whether nateglinide (meglitinide analogue) or valsartan (angiotensin II receptor antagonist) reduce the risk of cardiovascular events in individuals with impaired glucose tolerance and either existing cardiovascular disease (if 50 years or older) or with at least one additional cardiovascular risk factor (if 55 years of age or older). Details of the cardiovascular risk and inclusion criteria have been listed elsewhere.[14] Participants were recruited from 806 centres in 40 different countries. 42 149 patients were screened for inclusion. 32 843 patients were subsequently excluded, mainly because they did not meet the protocol-defined criteria for impaired glucose tolerance, leaving 9306 patients who were enrolled in the study between January, 2002, and January, 2004, and randomised [1:1:1:1] to one of the four treatment combinations. Participants were followed up for an average of 6 years.

Procedures

At baseline, all individuals underwent a detailed clinical assessment, including: oral glucose tolerance test (fasting and 2 h post-challenge glucose) and measurement of lipid profile (triglycerides, total cholesterol, and HDL and LDL cholesterol), renal function (urine albumin, creatinine, and sodium), blood and pulse pressure, electrocardiograph, bodyweight, and height. A detailed medical history was also recorded, including previous cardiovascular disease and concomitant diseases or conditions, smoking history, and medication status. Biochemical and anthropometric measures were repeated every year (apart from lipid factors which were only measured universally at 3 years onwards). All outcomes were assessed using the same standard operating procedures across sites.

All randomisation groups participated in a lifestyle modification programme that was designed to help participants achieve and maintain a 5% weight loss, reduce the amount of saturated and total fats in their diet, and increase their physical activity to 150 min a week. Personnel within each study site were trained to administer the programme and provided materials to participants at each clinic visit within the first 12 months (at 0·5, 1, 3, 6, and 12 months), with additional reinforcement undertaken through interim telephone contacts.

Habitual ambulatory activity was objectively assessed using a pedometer. Research-grade pedometers (Accusplit, San Jose, CA, USA), which assess purposeful steps taken through a horizontal, spring-suspended lever arm which moves up and down with each step, were dispatched to all NAVIGATOR study centres. 2 weeks after the initial baseline clinical measurements, participants were fitted with a pedometer and instructed to wear it during waking hours for 7 consecutive days. Participants were given a log book and instructed to write down their daily step count at the end of each day. Participants then returned their step log to the study team. Ambulatory activity levels were reassessed using the same criteria at 12 months.

Dietary behaviour was measured by a six-item questionnaire assessing whether participants included fruit and vegetables in their diet on a daily basis and whether they actively limited the amount of total fat, saturated fat, sugar, salt, and alcohol (to two drinks per day or fewer) in their diet.

For the purposes of this study, a single cardiovascular composite of time to death from cardiovascular causes or non-fatal myocardial infarction or non-fatal stroke was used. An independent committee, who were blinded to study allocation and ambulatory activity level, adjudicated all putative cardiovascular events.[15,16]

Statistical analysis

Ambulatory activity was measured as the average number of steps taken per day (total summed pedometer counts divided by the number days that data were captured). Change in ambulatory activity was calculated by subtracting average pedometers counts at 12 months from those at baseline. To remove potentially spurious data, baseline pedometer counts were truncated at 20 000 steps per day, representing roughly the 99th percentile. Change results were truncated at plus or minus 10 000 steps per day (ie, those with daily pedometer values outside these ranges were limited to these upper levels); roughly equivalent to the first and 99th percentile. Those reporting an average of zero steps per day at baseline (n=343) or 12 months (n=547) were counted as missing.

Biochemical, anthropometric, and behavioural variables are reported by category of change in ambulatory activity (more than 1500 step per day decrease, 0–1500 step per day decrease, 1–1500 step per day increase, or more than 1500 step per day increase), which were approximate to quartiles of change. Continuous variables are reported as median (IQR); categorical variables are reported by proportion.

Cox proportional hazard models were used to estimate the association between change in ambulatory activity and the risk of a subsequent cardiovascular event. Therefore, follow-up for cardiovascular events was initiated from a landmark at the 12-month visit and continued until a cardiovascular outcome or censoring for mortality, loss to follow up, or study completion. Baseline pedometer counts and change in pedometer counts were entered into the same model. Model 1 was adjusted for randomised treatment, body-mass index, and baseline demographic, biochemical, and clinical factors found to significantly affect the risk of subsequent cardiovascular events in the NAVIGATOR cohort.[17] We also tested whether individual dietary behaviours and medication (antihypertensive, aspirin, lipid-lowering)

status at baseline, factors not previously considered,[17] were related to cardiovascular events and should therefore be included in the model. These additional factors were included in the full model, and a backward selection process was used to determine association with the outcome at the level of p=0·05; only antihypertensive medication status was selected and consequently included as a covariate in model 1.

Model 2 was adjusted for the same covariates, as well as change in body-mass index between baseline and 12 months to investigate the extent to which any observed association was explained by change to bodyweight status. Model 3 was adjusted for the same variables as model 2; additionally, backward selection was again used to assess whether changes to health status and behaviour between baseline and 12 months were further associated with the cardiovascular event rate and hence potentially confounding results. Occurrence of unstable angina between baseline and 12 months and changes between baseline and 12 months in systolic blood pressure, 2 h glucose, estimated glomerular filtration rate, albumin/creatinine ratio, antihypertensive use, aspirin use, lipid-lowering agent use (actual lipid values were not measured at 12 months), and dietary responses were assessed. Estimated glomerular filtration rate at 12 months (representing change given baseline levels were already included) and the occurrence of unstable angina during the first 12 months were further selected and included in model 3.

To make use of the complete NAVIGATOR cohort, multiple imputation was used. Missing pedometer or covariate values at baseline or 12 months were imputed using Markov Chain Monte Carlo and regression methods. 25% of the cohort had missing pedometer data at baseline and 45% had missing data at 12 months; less than 3% of data were missing for other covariates. Final estimates reflect the combined analysis over five imputed datasets and account for the reduction in information due to missing data. Linearity assumptions and proportional hazards assumptions were checked. No violations were applicable.

We also undertook interaction analysis to assess whether associations between change in ambulatory activity and cardiovascular events were modified by baseline level of ambulatory activity, previous history of cardiovascular disease (myocardial infarction, unstable angina, other forms of coronary heart disease, congestive heart failure, percutaneous coronary intervention, coronary artery bypass graft surgery, or stroke), sex, region (Asian *vs* other), and age.

Adjusted event rates at 5 years were used to show the relation between change in ambulatory activity and cardiovascular events, using the average covariate value for adjustment covariates. Adjusted survival curves, using the corrected group prognosis method, were plotted by quartiles of change. Analysis was two-sided; p<0·05 was considered significant for main effects and p<0·1 was considered significant for interactions. Statistical analyses were done with SAS (version 9.2).

To investigate whether imputation affected the results, the above analysis was repeated for the subset of participants with complete data. Hazard ratios were compared with those generated from the full NAVIGATOR cohort. In addition, sensitivity analysis was undertaken to investigate whether results were affected if those with a non-fatal cardiovascular event occurring in the first 12 months or those classified as smokers at baseline were excluded from the analysis.

Role of the funding source

The NAVIGATOR study was sponsored by Novartis Pharmaceuticals and was designed by an academic executive committee in collaboration with the sponsor. All statistical analyses were done independently by statisticians at the Duke Clinical Research Institute (Durham, NC, USA). The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Follow-up data for cardiovascular events were available for 9018 participants over an average of 5 years after the 12-month landmark; characteristics including those with imputed data, are given in the appendix. Compared to patients with complete pedometer data at baseline and 12 months, those with missing pedometer data across at least one timepoint were more likely to be from Europe (55·0% [2568 of 4673] for missing data *vs* 50·8% [2209 of 4345] for complete data) or North America (25·4% [1189 of 4673] *vs* 19·5% [846 of 4345]), a smoker (11·4% [535 of 4673] *vs* 10·0% [434 of 4345]), and were less likely to have a previous history of congestive heart failure (26·5% [1238 of 4673] *vs* 29·9% [1298 of 4345]). There was no difference in blood pressure or other biochemical risk factors, including lipid and glucose parameters.

See Online for appendix

The baseline characteristics of those with both baseline and 12-month data are displayed by category of change in table 1. Baseline levels of ambulatory activity were highest in those with the greatest decrease in activity at 12 months. In the cohort as a whole, average pedometer levels were similar at baseline (median 5892 [IQR 735–8739]) and follow-up (6320 [3988–8978]); however, there was substantial inter-individual variation in change (truncated range –10 000 to 10 000 steps per day). In total, there were 531 cardiovascular events during 45 211 person-years of follow-up.

Table 2 shows the hazard ratios for the association of baseline ambulatory activity and change in ambulatory activity with cardiovascular events. After adjustment for each other and measured confounding variables, both

	Category 1 (decrease of more than 1500 steps per day) N=1099	Category 2 (decrease between 1 and 1500 steps per day) N=1068	Category 3 (increase between 0 and 1499 steps per day) N=1097	Category 4 (increase of at least 1500 steps per day) N=1081	Overall N=4345
Characteristics					
Age, years	63 (58–68)	64 (58–69)	64 (58–69)	62 (58–68)	63 (58–68)
Women	538 (49·0%)	576 (53·9%)	569 (51·9%)	551 (51·0%)	2234 (51·4%)
Region					
Asia	129 (11·7%)	70 (6·6%)	74 (6·7%)	91 (8·4%)	364 (8·4%)
Europe	559 (50·9%)	550 (51·5%)	562 (51·2%)	538 (49·8%)	2209 (50·8%)
Latin America	211 (19·2%)	173 (16·2%)	174 (15·9%)	221 (20·4%)	779 (17·9%)
North America	174 (15·8%)	238 (22·3%)	242 (22·1%)	192 (17·8%)	846 (19·5%)
Other	26 (2·4%)	37 (3·5%)	45 (4·1%)	39 (3·6%)	147 (3·4%)
Race					
White	836 (76·1%)	881 (82·5%)	906 (82·6%)	889 (82·2%)	3512 (80·8%)
Black	16/ (1·5%)	17 (1·6%)	18 (1·6%)	13 (1·2%)	64 (1·5%)
Oriental	136 (12·4%)	75 (7·0%)	75 (6·8%)	98 (9·1%)	384 (8·8%)
Other	111 (10·1%)	95 (8·9%)	98 (8·9%)	81 (7·5%)	385 (8·9%)
Current smoker	105 (9·6%)	100 (9·4%)	120 (10·9%)	109 (10·1%)	434 (10·0%)
Clinical history					
Congestive heart failure	40 (3·6%)	48 (4·5%)	42 (3·8%)	42 (3·9%)	172 (4·0%)
Coronary heart disease*	298 (27·1%)	354 (33·1%)	315 (28·7%)	331 (30·6%)	1298 (29·9%)
Cerebrovascular disease†	92 (8·4%)	85 (8·0%)	92 (8·4%)	95 (8·8%)	364 (8·4%)
Pulmonary disease‡	9 (0·8%)	19 (1·8%)	9 (0·8%)	7 (0·6%)	44 (1·0%)
Peripheral artery disease§	22 (2·0%)	44 (4·1%)	37 (3·4%)	30 (2·8%)	133 (3·1%)
Chronic obstructive pulmonary disease	51 (4·6%)	45 (4·2%)	60 (5·5%)	48 (4·4%)	204 (4·7%)
Hypertension	888 (80·8%)	850 (79·6%)	878 (80·0%)	871 (80·6%)	3487 (80·3%)
Family history of premature coronary heart disease	162 (14·7%)	176 (16·5%)	174 (15·9%)	162 (15·0%)	674 (15·5%)
Family history of diabetes	398 (36·2%)	392 (36·7%)	400 (36·5%)	379 (35·1%)	1569 (36·1%)
Clinical features					
Body-mass index, kg/m²	28·8 (26·1–32·4)	29·6 (26·7–33·4)	29·6 (26·7–33·1)	29·5 (26·8–32·9)	29·4 (26·6–33·0)
Systolic blood pressure, mm Hg	140 (129–150)	140 (128–150)	140 (129–150)	140 (129–150)	140 (129–150)
Diastolic blood pressure, mm Hg	82 (77–90)	82 (76–90)	82 (76–90)	82 (77–90)	82 (76–90)
Pulse pressure, mm Hg	55 (48–65)	56 (48–65)	56 (48–65)	57 (48–65)	56 (48–65)
Atrial fibrillation or flutter	29 (2·6%)	45 (4·2%)	41 (3·7%)	46 (4·3%)	161 (3·7%)
Laboratory variables					
Fasting glucose, mmol/L	6·1 (5·7–6·5)	6·1 (5·7–6·5)	6·1 (5·7–6·4)	6·1 (5·7–6·4)	6·1 (5·7–6·4)
2 h glucose, mmol/L	9·1 (8·4–9·9)	9·1 (8·4–9·9)	9·0 (8·3–9·9)	9·0 (8·3–9·9)	9·0 (8·4–9·9)
Total cholesterol, mmol/L	5·39 (4·67–6·15)	5·33 (4·65–6·05)	5·33 (4·69–6·04)	5·40 (4·75–6·13)	5·36 (4·68–6·10)
HDL cholesterol, mmol/L	1·24 (1·06–1·48)	1·23 (1·03–1·47)	1·26 (1·03–1·48)	1·20 (1·01–1·45)	1·24 (1·03–1·47)
LDL cholesterol, mmol/L	3·27 (2·68–3·91)	3·18 (2·56–3·82)	3·15 (2·56–3·86)	3·27 (2·63–3·96)	3·23 (2·61–3·89)
Triglycerides, mmol/L	1·64 (1·20–2·26)	1·68 (1·24–2·37)	1·70 (1·20–2·42)	1·74 (1·24–2·43)	1·69 (1·22–2·36)
Haemoglobin, g/L	146 (138–155)	146 (138–154)	147 (139–155)	146 (138–155)	146 (138–155)
eGRF, mL/min/1·73m²	82·5 (70·5–95·0)	78·2 (68·0–89·9)	79·4 (68·4–90·7)	78·7 (67·9–91·9)	79·9 (68·8–92·1)
Urine albumin/creatinine ratio, mg/mmol	0·78 (0·50–1·58)	0·77 (0·49–1·60)	0·79 (0·50–1·47)	0·76 (0·49–1·55)	0·77 (0·50–1·54)
Sodium, mmol/L	142 (141–144)	142 (141–144)	142 (141–144)	142 (141–144)	142 (141–144)
Medications					
Lipid lowering agent	394 (35·9%)	449 (42·1%)	422 (38·5%)	372 (34·4%)	1637 (37·7%)
Antihypertensives	779 (70·9%)	769 (72·1%)	781 (71·3%)	763 (70·6%)	3092 (71·2%)
Aspirin	366 (33·3%)	391 (36·6%)	401 (36·6%)	394 (36·4%)	1552 (35·7%)
Electrocardiogram					
Clinically insignificant abnormality	384 (35·5%)	402 (38·2%)	416 (38·7%)	377 (35·3%)	1579 (36·9%)
Clinically significant abnormality	164 (15·2%)	182 (17·3%)	163 (15·1%)	189 (17·7%)	698 (16·3%)
Dietary behaviour					
Limited total fat	810 (74·1%)	757 (71·2%)	762 (70·1%)	756 (70·5%)	3085 (71·5%)

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	Category 1 (decrease of more than 1500 steps per day) N=1099	Category 2 (decrease between 1 and 1500 steps per day) N=1068	Category 3 (increase between 0 and 1499 steps per day) N=1097	Category 4 (increase of at least 1500 steps per day) N=1081	Overall N=4345
(Continued from previous page)					
Limited saturated fat	818 (74·8%)	788 (74·1%)	787 (72·4%)	785 (73·2%)	3178 (73·6%)
Included fruit/vegetable every day	919 (84·1%)	902 (84·9%)	918 (84·5%)	911 (84·9%)	3650 (84·6%)
Limited sugar	812 (74·3%)	757 (71·2%)	775 (71·3%)	785 (73·2%)	3129 (72·5%)
Limited salt	801 (73·3%)	712 (67·0%)	748 (68·9%)	701 (65·3%)	2962 (68·6%)
Limited alcohol (≤2 drinks/day)	963 (88·5%)	925 (87·3%)	934 (86·1%)	910 (85·0%)	3732 (86·7%)
Pedometer					
Baseline pedometer count	9325 (6687–11887)	5778 (3766–8167)	5338 (3386–7806)	5156 (3212–7612)	6245 (4065–9157)

Continuous variables are median (IQR). Categorical variables are n (%). *Myocardial infarction, angina, positive stress test, or coronary revascularisation. †Stroke, transient ischaemic attack. ‡Pulmonary embolism or deep venous thrombosis. §Limb or foot amputation, intermittent claudication, limb arterial bypass procedure.

Table 1: **Baseline patient characteristics by category of change in ambulatory activity level from baseline to 12 month follow-up, reported for the subset of participants with complete baseline and follow-up data**

baseline ambulatory activity and change in ambulatory activity between baseline and 12 months were significantly and inversely associated with the risk of a cardiovascular event. Specifically, at baseline, each 2000 step per day increment in ambulatory activity was associated with a 10% lower cardiovascular event rate. For change, each 2000 step increase or decrease in daily ambulatory activity from baseline to 12 months was associated with an additional 8% lower or higher cardiovascular event rate, respectively. Results were unaffected when further adjusted for change in body-mass index, change in estimated glomerular filtration rate, and the occurrence of unstable angina between baseline and 12 months.

Interaction analysis revealed results for change in ambulatory activity were not modified by baseline value (p=0·58), indicating that for each given unit of increase in ambulatory activity, there were similar effects on cardiovascular risk irrespective of where participants started at baseline. Furthermore, results were not modified by a previous history of cardiovascular disease (p=0·62), sex (p=0·66), age (p=0·14), or region (p=0·72 for Asia *vs* other). However, the small sample size from the Asia region resulted in a wide CI for the estimated hazard ratio ([HR] 0·97; 95% CI 0·73–1·28), therefore the p value for region should be interpreted with caution.

The figure shows adjusted estimates of the cardiovascular event rate by change in ambulatory activity as a continuous variable, bounded by the 5th and 95th percentile. The adjusted survival estimates representing the risk of a cardiovascular event by quartile of change in ambulatory activity are shown in the appendix.

Results were unaffected (less than 3% difference in hazard ratios) when analyses were repeated on the subsample with complete pedometer and covariate data (appendix); however, significance levels were increased because of the reduced sample size (HR 0·90; 95% CI 0·81–1·01; p=0·0606 per 2000 steps a day change for the fully adjusted model). The hazard ratios were similarly unaffected if those with a non-fatal cardiovascular event occurring within the first 12 months (n=93) or those classified as smokers at baseline (n=969) were excluded (appendix).

	HR	95% CI	p
Model 1			
Baseline ambulatory activity (2000 step per day increment)*	0·90	0·84–0·96	0·0014
Change in ambulatory activity from baseline to 12 months (per 2000 step per day difference in change)*	0·92	0·86–0·99	0·0271
Model 2			
Baseline ambulatory activity (2000 step per day increment)*	0·90	0·84–0·96	0·0017
Change in ambulatory activity from baseline to 12 months (per 2000 step per day difference in change)*	0·92	0·86–0·99	0·0321
Model 3			
Baseline ambulatory activity (2000 step per day increment)*	0·90	0·84–0·96	0·0021
Change in ambulatory activity from baseline to 12 months (per 2000 step per day difference in change)*	0·92	0·86–0·99	0·0349

*Baseline ambulatory activity and change in ambulatory activity were included in the same model. Model 1: adjusted for randomised treatment group and the following variables at baseline: body-mass index, age, region (North America, Europe, Asia, Latin America, other), sex, current smoker status, coronary heart disease composite (previous myocardial infarction, angina, positive stress test, or coronary revascularisation), cerebrovascular composite (stroke, transient ischaemic attack), significant abnormal electrocardiogram, insignificant abnormal ECG, albumin/creatinine ratio, pulmonary composite (pulmonary embolism or deep venous thrombosis), peripheral artery disease composite (limb or foot amputation, intermittent claudication, limb arterial bypass procedure), congestive heart failure, chronic obstructive pulmonary disease, pulse pressure, temporary atrial fibrillation or flutter, sodium, estimated glomerular filtration rate (eGFR), haemoglobin, LDL-cholesterol, and antihypertensive medication use. Model 2: adjusted for the above variables plus change in body-mass index from baseline to 12-months. Model 3: adjusted for the above variables plus change in body-mass index, the occurrence of unstable angina between baseline and 12 months and change in eGFR between baseline and 12 months.

Table 2: **Association of baseline and change in daily ambulatory activity with cardiovascular events (composite of cardiovascular mortality, stroke, or myocardial infarction)**

Discussion

Both baseline ambulatory activity and change in ambulatory activity over 12 months were associated independently with the risk of a cardiovascular event in the ensuing 5 years. Specifically, every 2000 step per day increment in ambulatory activity at baseline (roughly equivalent to 20 min a day of moderately-paced walking activity[18]) was associated with a 10% lower risk of a

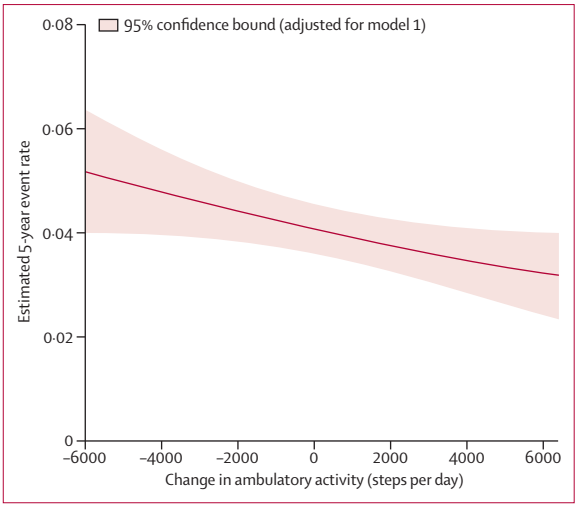

Figure: **Relation between change in ambulatory activity and adjusted 5-year cardiovascular event rates**

***Panel*: Research in context**

Systematic review

We searched PubMed, Medline, and Google Scholar with the search terms "physical activity", "exercise", "mortality", and "cardiovascular". We were unable to identify any studies that examined the association between objectively assessed physical activity and cardiovascular events. Recent studies have reported meta-analyses of observational studies looking at the effect of self-reported physical activity and non-vigorous physical activity on the risk of cardiovascular disease and mortality.[8–10] However, because of the nature of the self-reported instruments used within the included studies, the reviews were unable to adequately quantify the amount of physical activity needed to gain specific benefits. Moreover, the association between change in physical activity and cardiovascular disease has not been investigated in high-risk adults.

Interpretation

In this study involving adults at high risk of type 2 diabetes and cardiovascular disease, every 2000 step per day increment in ambulatory activity at baseline was associated with a 10% lower risk of a cardiovascular event and each 2000 step per day change from baseline to 12 months was associated with an additional 8% difference in the cardiovascular event rate. Results for change remained consistent across men and women, region, age, and baseline level of activity.

cardiovascular event. Moreover, each 2000 step per day change from baseline to 12 months was associated with an additional 8% difference in the cardiovascular event rate. This difference was unaffected when further adjusted for change in body-mass index and other potential confounding factors at 12 months. Results were not modified by sex, age, level of baseline activity, or pre-existing cardiovascular disease. To our knowledge, this is the first study to investigate the association between daily ambulatory activity and cardiovascular events in at-risk adults (panel).

Walking is known to be the most common and preferred choice of physical activity,[19–21] and behaviour change programmes aimed at increasing total daily ambulatory activity through pedometer use have been highly effective across a broad range of groups, including those with impaired glucose tolerance.[22,23] However, the effect of changing overall daily ambulatory activity levels on cardiovascular events has not been elucidated by controlled intervention studies. This observational study therefore extends previous research by suggesting that baseline ambulatory activity and change in ambulatory activity are both important and independent determinants of future cardiovascular disease in high-risk adults. Moreover, the lack of an interaction between the association of baseline and change in ambulatory activity with future cardiovascular events suggests that the relative benefit of increased ambulatory activity, or deleterious effect of decreased ambulatory activity, remains consistent irrespective of the starting level. These findings support both the promotion of increased ambulatory activity, and the avoidance of decreased ambulatory activity irrespective of the starting level, as important targets in the prevention of chronic disease.

The relation between change in ambulatory activity and cardiovascular events remained significant after adjustment for both baseline body-mass index and change in body-mass index. Previous smaller observational studies using objective measures of ambulatory activity or total physical activity have provided equivocal evidence on whether the relation between physical activity and cardiometabolic risk factors are mediated through adiposity.[24–27] By contrast, large observational studies that have shown a strong inverse dose-response relation between objectively assessed cardiorespiratory fitness and cardiovascular events after adjustment for body-mass index.[28,29] However, cardiorespiratory fitness is determined by multiple factors, not just physical activity. Our study therefore provides novel evidence for the cardioprotective role of daily ambulatory activity, independent of bodyweight status. This observational finding is strengthened by several biological mechanisms that have consistently been linked to increased physical activity, including improved lipid metabolism, change in low-density lipoprotein particle size, increased tissue plasminogen activator activity, and decreased coronary artery calcium.[30]

This study has several strengths. First, the analysis was adjusted for a comprehensive list of possible confounding variables, both at baseline and 12 months, shown to be related to cardiovascular events in this cohort. Second, the sample comprised a large international population with impaired glucose tolerance and at high cardiovascular risk, making the results broadly generalisable to diabetes and cardiovascular disease prevention programmes globally. Third, the large study cohort was recruited over a relatively short time frame (2 years), minimising the possibility of temporal factors affecting the results. Finally, in the absence of randomised controlled trials assessing the effect of physical activity on morbidity or mortality outcomes, this study represents

an advance in quantifying the impact of daily ambulatory activity on cardiovascular events in a high-risk population.

The main limitation was the large amount of missing pedometer data at baseline and 12 months. This was addressed using rigorous multiple imputation techniques which allowed use of adjustment variables from the full dataset. Sensitivity analysis also revealed no meaningful difference between estimates generated from the complete case dataset. Nonetheless, imputation might not completely account for missing data, which potentially limits generalisability. Limitations also exist in the use of pedometers; participants were not blind to pedometer output and were asked to record their daily ambulatory activity in a log book and physical activity intensity, mode, and wear-time were not assessed. Many of these limitations could have affected recorded levels of ambulatory activity. For example, higher ambulatory activity might indicate greater measurement reactivity due to self-recording daily step counts or better compliance to the measurement protocol through greater wear time. This would act to increase inter-individual or intra-individual variation as well as introducing the possibility that characteristics related to pedometer use beyond total ambulatory activity were confounding the results. Furthermore, cardiorespiratory fitness was not assessed; however, other studies have shown that changes in habitual physical activity and cardiorespiratory fitness are weakly correlated and independently associated with metabolic health.[25] In view of the high-risk nature of the cohort, the results are also not generalisable to the general population. Finally, because of the observational design, we were unable to establish causation between ambulatory activity and cardiovascular disease. Unmeasured or imprecisely measured lifestyle or related factors could have acted to confound associations. Similarly, the design cannot fully negate the possibility of reverse causation. However, the graded association between change in ambulatory activity and cardiovascular risk, the fact that the analysis was controlled for a comprehensive list of possible confounding variables, and biological plausibility all provide indirect support for the importance of physical activity in the promotion of long-term cardiovascular health.

This study provides novel evidence that both the overall level of daily ambulatory activity and change in ambulatory activity over 12 months display a graded inverse association with the risk of cardiovascular disease in high-risk individuals with impaired glucose tolerance, even after adjustment for multiple confounding variables and body-mass index. In the absence of randomised controlled studies assessing the effect of physical activity on morbidity or mortality outcomes, our findings strengthen the evidence underpinning the importance of physical activity in the promotion of cardiovascular health and have important implications for public health recommendations and the prevention of chronic disease. Implications extend to the importance of preventing a decline in physical activity levels in middle-aged and elderly populations.

Contributors

SMH, WEK, TY, LT, KMH, CWB, JT, and MJD were responsible for the study concept and design. LT and PJS had access to all the data and undertook the statistical analysis. TY drafted the manuscript. All authors contributed to the content and critical revision of the manuscript.

Conflicts of interest

SMH is a member of the NAVIGATOR executive committee. CWB is paid an honorarium for her role as the Editor of the Journal of Nutrition in Geriatrics and Gerontology and as a contributing editor to the Duke Health Newsletter. RMC has received consulting fees from Bayer, Bristol-Myers Squibb, CV Sight LLC, DSI-Lilly, Gambro, theHeart.org, Janssen, Kowa, Novartis, Pfizer, Regeneron, and Roche, and his institution has received research grants from Bristol-Myers Squibb, Novartis, Amylin, Merck, Schering-Plough, Scios, Johnson & Johnson, and Eli Lilly. RRH has received research support from Amylin, Bayer, Merck, and Novartis; attended advisory boards with Amylin, Lilly, Merck, Novartis, and Novo Nordisk; and given lectures supported by Bayer, Lilly, Merck, and Novo Nordisk. MAB has received research support from Novartis and Bayer, and her department has received research funding from Merck, Amylin, Lilly, and BMS. JT has received research support from AstraZeneca, Merck Sharp & Dohme, Novartis, and Servier, and has acted as a consultant, advisory board member, or speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Serono, and Merck Sharp & Dohme. MJD has acted as a consultant, advisory board member, and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, and Roche, and her department has received research grants from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Merck Sharp & Dohme, Johnson & Johnson, and GlaxoSmithKline. The other authors declare that they have no conflicts of interest.

Acknowledgments

TY and MD are supported by the NIHR Leicester-Loughborough Diet, Lifestyle, and Physical Activity Biomedical Research Unit, Leicester, UK.

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