The Protective Effect of time spent walking on Risk of Stroke in Older Men.

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Abstract

Background and Purpose: Older adults have the highest risks of stroke and the lowest physical activity (PA) levels. It is important to quantify how walking (the predominant form of PA in older age) is associated with stroke.

Methods: 4252 men from a UK population-based cohort reported usual PA (regular walking, cycling, recreational activity and sport) in 1998-2000. Nurses took fasting blood samples and made anthropometric measurements.

Results: Among 3435 ambulatory men free from CVD and heart failure in 1998-2000, 195 first strokes occurred during 11 years follow-up. Men walked a median of 7 (IQR 3-12) hours/week; walking more hours was associated with lower heart rate, D-dimer and higher FEV_1. Compared to men walking 0-3 hours/week, men walking 4-7, 8-14, 15-21 and >22 hours, had age and region adjusted Hazard Ratios(HRs) (95%CIs) for stroke of 0.89(0.60,1.31), 0.63(0.40,1.00), 0.68(0.35,1.32), and 0.36(0.14,0.91) respectively, p (trend)= 0.006. HRs were somewhat attenuated by adjustment for established and novel risk markers (inflammatory and hemostatic markers and cardiac function [NT-proBNP]) and walking pace, but linear trends remained. There was little evidence for a dose response relationship between walking pace and stroke; comparing average pace or faster to a baseline of slow pace, the HR for stroke was 0.65 (95%CI 0.44, 0.97), which was fully mediated by time spent walking.

Conclusions: Time spent walking was associated with reduced risk of onset of stroke in dose response fashion, independent of walking pace. Walking could form an important part of stroke prevention strategies in older people.

Introduction:

Stroke is a major cause of disability and mortality at older ages, so preventive strategies are important[1]. Physical activity (PA) in middle age is protective against stroke; a meta-analysis reported that high compared to low PA levels were associated with overall 19% lower risk of stroke, although previous findings are mixed, with some inverse, u-shape and even positive associations[2]. Some studies suggest that PA may be more protective against stroke at older ages than in middle age[3, 4]. Walking is a predominant form of PA in older adults[5]. It is therefore important to understand whether and how walking is related to onset of stroke in older adult populations, which have high risks of stroke and low activity levels.

Whilst slower walking speeds and spending less time walking are associated with elevated total cardiovascular disease (CVD) mortality risk[6], few prospective studies of stroke examine the relative importance of pace compared to time spent walking or distance walked[7]. Some suggest that both faster walking pace and greater time spent walking[3, 7, 8] or MET hours[9] of walking are protective against stroke and others have examined only walking speed[10, 11]. It is not clear what factors may mediate associations between walking and onset of stroke. To our knowledge, existing prospective studies of walking and stroke risk have not systematically addressed the mediating roles of novel cardiovascular markers[2], including C-Reactive Protein (CRP) a marker of inflammation, D-dimer a marker of coagulation and fibrinolysis and NT-ProBNP a marker of cardiac dysfunction, each of which is strongly related to onset of stroke[12-14] and also to PA level[15, 16].

We therefore test the hypotheses that (i) walking (pace, time spent and distance), and (ii) total leisure time PA are protective against onset of stroke. We investigate the role of CRP, D-dimer and NT-ProBNP alongside traditional risk factors as intermediate pathways.

Methods

Study Population

The British Regional Heart Study is a prospective cohort of 7735 men recruited from a single Primary care centre in each of 24 British towns in 1978-80 (age 40-59 years). Men were followed up for stroke morbidity and all-cause mortality. In 1998-2000 4252 participants (aged 60-79 years) attended for follow-up measurements (77% response rate)[17]. 811 with pre-existing MI, stroke or heart failure and 6 confined to a wheelchair were excluded to reduce potential for reverse causality, leaving 3435 men.

Clinical data, ethical approval

Men completed questionnaires and nurses measured height, weight, blood pressure and FEV_1 (forced expiratory volume in one second)[17] and recorded an ECG[12] (including resting heart rate) and Minnesota coding criteria were used to define atrial fibrillation (8.3.1 and 8.3.3) and definite and possible left ventricular hypertrophy (3.1 and 3.3). Fasting venous blood samples were collected and analysed for total and HDL-cholesterol, triglycerides[18] and vitamin C[19]. CRP was assayed by ultrasensitive nephelometry (Dade Behring). Plasma levels of D-dimer were measured with ELISA (Biopool AB), as was von Willebrand factor (vWF) antigen (DAKO). NT-proBNP was measured using the Elecsys 2010 electrochemiluminescence method (Roche diagnostics, Burgess Hill, United Kingdom)[13]. All relevant local research ethics committees provided ethical approval and all men provided informed written consent to the investigation.

Assessment of physical activity

In 1998-2000 men self-reported usual pattern of PA under the headings of regular daily walking or cycling, recreational activity, and sporting (vigorous) activity. Men reported usual walking during an average week (i) duration: number of hours spent on all forms of walking, (ii) distance: number of miles walked in total (iii) pace: slow, steady average, fairly brisk and fast (at least 4 mph). Men reporting recreational and sporting activity were classified according to whether or not they participated in vigorous activities at least once a month. Recreational activity including eg gardening, pleasure walking (hiking), and do-it-yourself jobs. Sporting activity included eg running, golf, swimming and tennis. A PA score (validated in relation to heart rate and FEV_1[16, 20]) was derived for each man on the basis of frequency and type (intensity) of each activity, scored based on intensity and energy demands using Minnesota intensity codes. The score included duration of walking but not distance walked or walking pace. Questionnaire data was available for 3357/3435 (98%) about walking pace, 2995/3435 (87%) for hours walked per week and 3231 (94%) for distance walked per week; men with missing data for pace, distance or time spent walking were dropped from relevant analyses.

Case ascertainment and follow-up

The outcome was first fatal or non-fatal stroke occurring following the 1998-2000 survey up to June 2010. Fatal cases were ascertained through the National Health Services Central Registers (death certificates with ICD-9 codes 430-438 for stroke, indicating deaths with cerebrovascular disease as the underlying cause). Non-fatal stroke events were those that produced a neurological deficit that was present for >24 hours; data about non-fatal events was obtained from two-yearly reviews of patient primary care notes (including all hospital

and clinic correspondence). Supplementary information from CT/MRI scans to confirm diagnoses was available in a subset of men.

Statistical methods

Means, medians or proportions of behavioural and demographic factors selected *a priori* were calculated according to usual walking (i) pace (ii) duration (iii) distance reported at Q20. Linear regression analyses were used to test trends across the walking categories. Skewed variables were natural log-transformed. Variables exhibiting significant diurnal variation were adjusted for time of measurement . Blood pressure (BP) and body mass index (BMI) were adjusted for intra-observer variation.

Cox proportional hazards regression models were used to estimate associations between Q20 walking measures and risk of stroke. Survival times were censored at date of stroke, death from any cause, or end of follow-up period, whichever occurred first. Date of entry into the study in 1999-2000 was used as the time origin. The proportional hazards assumption was examined using time varying covariates, calculating interactions of predictor variables and a function of survival time and including them in the models. Examination of time varying covariates indicated that proportionality assumptions were not violated. The Hazard Ratios (HRs) for categories of walking in 1999-2000 were estimated and the overall association was tested with the continuous association between walking (i) time (ii) distance and (iii) pace and stroke risk, adjusted for gender, age (continuous variable) and region of residence. Time and duration of walking were adjusted for pace, and pace adjusted for time. Models were also adjusted for participation in vigorous recreational or sporting activities. Models were next adjusted for covariates associated with both stroke and walking; established risk factors (alcohol and tobacco use, social class [based on occupational group "manual" (skilled

manual, unskilled or partly skilled) or "non-manual" (professional, managerial, technical, skilled non-manual occupations)]), then biological risk factors (as continuous variables): first BMI and then systolic blood pressure (SBP), total and HDL cholesterol (HDL-C) and triglycerides, next FEV_1 was added, finally, novel risk markers, CRP, D-dimer and NT-ProBNP were added. Interactions were tested using likelihood ratio tests (LRT). Analyses were repeated excluding the first two years of follow-up.

Results

Analyses are based on 3357 ambulatory men (mean age 68.3 years) who were free from CHD, stroke and heart failure at entry. Men walked a median of 7 hours per week (interquartile range 3-12 hours). The correlation between categories of hours walked and walking pace was r=0.08 ($p<0.001$) and hours walked and walking distance was r=0.22 ($p<0.001$). Men who walked for more hours per week were younger, more likely to be of manual social class, reported higher levels of usual PA, had faster walking pace and reported walking more miles per week than those who walked for fewer hours. The men who walked for more hours had lower heart rate, D-dimer and higher FEV_1 (Table 1).

Men reported usual walking pace as slow (13%, n=425), steady average (64%, n=2143) and fairly brisk or fast (24%, n=789). Men with faster compared to slower walking pace were more likely to be younger, non-manual social class, never smokers, light drinkers, had higher usual PA levels, walked for more hours per week and longer distances, and had lower prevalence of diabetes (Supplementary Table 1). Faster walking pace showed graded associations with lower BMI, waist circumference, plasma vitamin C, HDL-cholesterol, triglycerides, systolic blood pressure, use of blood pressure lowering medications, heart rate,

and inflammatory markers CRP, vWF, D-dimer and NTpro-BNP. Men with a faster walking pace had a higher mean FEV_1.

During a median 10.9 years follow-up, 195 first stroke events occurred among 2995 men, 6.7(95%CI 5.8, 7.7) per 1000 person-years. The HRs for stroke reduced with increasing usual PA level, but confidence intervals (CIs) were wide (Table 2) and linear trends not significant. Focusing next on walking, we did not find evidence for an association between usual distance walked and stroke (Table 3), although the HR for men who walked the furthest distance (>=15 miles/week) was smallest, but CIs were wide. However, a strong inverse dose-response association was observed between time spent walking and risk of stroke (Table 4). Compared with men spending 0-3 hours/week walking, men who walked 4-7, 8-14, 15-21 and >22 hours had age and region adjusted HRs of 0.89(0.60,1.31), 0.63(0.40,1.00), 0.68(0.35,1.32), 0.36(0.14,0.91) respectively, p(linear trend)=0.006. Adjustments for multiple established risk factors including MVPA level (Model 2), walking pace (Model 3) and FEV_1 (Model 4), attenuated associations to a very small degree. CRP, D-dimer and NT-ProBNP each attenuated coefficients to a similar degree when adjusted separately (not presented) or together (Model 5), and the linear trend remained significant. We did not observe evidence for an interaction between time spent walking and pace (LRT, p=0.1). In sensitivity analyses excluding the first two years of follow-up time, the point estimates were similar with slightly wider CIs, but significant trends remained.

The risk of stroke was reduced for average pace compared to slow pace HR 0.66(0.43,0.99) with no further reduction for "fairly brisk" HR 0.64(0.39,1.07), so the average and fairly brisk were combined and compared to slow pace. The HR for stroke was significantly reduced in "average or brisk pace" compared to slow pace, 0.62(0.42, 0.92) for Model 2

(Table 5), but was fully mediated on adjustment for either walking distance; HR 0.67(0.44, 1.02), or duration; HR 0.67(0.43, 1.04).

Supplementary information on CT/MRI scans was available for 75/195 (39%) of cases; 64/75 (85%) were ischemic and 11/75 (15%) were hemorrhagic strokes. In sensitivity analyses of the 64 ischemic cases, the dose-response pattern of lower risk with more hours walked was observed (p[trend]=0.004), no associations were observed for the number of miles walked and the estimates for walking pace were similar to the main analyses.

Discussion

Among community dwelling older men, we observed a weak non-significant inverse association between total leisure time PA and stroke, and a strong inverse dose-response association between time spent walking and risk of stroke, independent of walking pace, MVPA, established and novel risk factors. Results suggest that the total volume of walking rather than the intensity is important for stroke prevention. We investigated a range of plausible mechanisms to explain associations between walking and stroke, including lipids, hypertension, markers of inflammation and endothelial dysfunction, but none fully mediated the associations with time spent walking.

Comparison with other studies

Findings about total PA and risk of stroke are mixed; inverse, u-shape and even positive associations are reported[2]. We found weak evidence for an inverse association between total leisure-time PA or vigorous activity with onset of stroke, fitting with other null findings for total leisure time activity in men[3, 8]. However a meta-analysis concluded that high levels of leisure time PA were associated with a 19% reduction in risk of stroke[2]; our estimates for

moderate and more intense activity are of similar magnitude, although our confidence intervals (CIs) were wide.

There is little epidemiologic evidence about walking pace and duration about stroke, most focuses on CHD and total CVD[6]. Our findings that time spent walking was associated with reduced risk of stroke fits with the few existing studies which include middle aged and older adults[3, 7-9], Hence our finding that time spent walking but not total PA was associated with stroke fits with other data; this consistency strengthens our speculation that it is a true biological finding, although we acknowledge that it could be due to issues with measurement of other types of PA. We did not find consistent evidence that walking pace was related to stroke onset; time spent walking explained the raised risk in slow-paced walkers. Nor did we find that distance walked protected against stroke, although distance may be harder to recall accurately than usual pace or time spent walking. A large volume of weekly walking could be a proxy for low levels of sedentary behavior. A recent study reported that sedentary behavior is associated with stroke independently of PA[21], although we cannot test this in our dataset.

Our study is novel in exploring mechanisms; we found that established stroke risk factors (including blood pressure and lipids) were weak mediators of the associations between time spent walking and stroke as were markers of inflammation(CRP), coagulation(D-dimer) and also cardiac injury(NT-proBNP). It is possible that associations between walking volume and ischemic stroke may be mediated through mechanisms related to progression of atherosclerosis and clot rupture that also act in CHD, whereas effects on hemorrhagic stroke may act through blood-pressure related mechanisms, but we could not test this hypothesis.

Strengths and limitations

This study benefits from prospective data with high follow-up rates, multiple measures of walking habit, (pace, time spent walking and distance) and other types of self-reported

habitual PA, combined in a score; both PA score[16, 20] and time spent walking are related to heart rate and FEV_1. It is possible that there is a small degree of overlap between the total PA score (which uses weekend pleasure walking plus other components) and the daily walking variable (designed to capture active transport), but given that walking is protective against stroke, but the total PA score is not, any overlap is unlikely to have biased the score. Future studies with objective PA measures may clarify the shape of the dose-response curve between activity volume and intensity (including sedentary behavior) and stroke risk better than self-report which may be subject to recall bias, yet self-reports are required for identifying activity types.

Whilst we cannot entirely exclude residual confounding as an explanation for our findings, we adjusted for a wide range of important behavioural and social confounders including other dimensions of walking and other types of physical activities. To reduce the risk of reverse causality, we excluded men with pre-existing physician diagnosed CVD, or confined to a wheelchair, as these men have increased mortality risks and are likely limit their PA due to their health. We also excluded the first two years of follow-up in sensitivity analyses. Unlike other studies of walking pace and duration, we could investigate the mediating role of novel and established biological risk factors which may be on the causal pathway between walking and stroke risk. We were able to distinguish between subtypes of stroke in a subset of cases, and, as reported elsewhere[12] ischemic strokes were more common than haemorrhagic strokes (a small minority) in older adults. In a sensitivity analysis of men with CT-confirmed ischemic stroke findings were similar to those for all participants. Our study examines only men, so we cannot generalize results to older women, however the sample is socio-economically representative of older men in the UK and has exceptionally high follow-up rates. One meta-analysis found borderline evidence for gender differences[22] and another reported that more vigorous PA may be required for protection against stroke in women than in men[2], but this may be because population levels of PA are lower in women than in men.

In conclusion, time spent walking was associated with risk of stroke in a dose-response fashion independent of walking pace and moderate to vigorous PA, indicating that among older men, daily walking could beneficially reduce risk of stroke. Therefore walking for more hours per week could form an important part of stroke-prevention strategies. Future studies using objective measures of habitual walking will shed more light on this question.

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DISCLOSURES: none

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Table 1 Characteristics of men according to time spent walking per week, (n=2995 men).

	1-3 hours/week (n=803)	4-7 hours/week (n=921)	8-14 hours/week (n=785)	15-21 hours/week (n=270)	>=22 hours/ week (n=216)	P (trend)*
Age	68.21	68.56	68.53	67.99	66.63	0.005
Social class % (n)						<0.001
Manual	45.6(365)	45.3(416)	48.7(381)	54.3(146)	64.4(139)	
Alcohol % (n)						0.081
>15 units/week	13.6(107)	17.0(153)	19.8(150)	16.2(43)	16.5(35)	
Tobacco % (n)						0.411
current smoker	13.0(104)	11.6(107)	13.4(105)	13.4(36)	17.1(37)	
Physical activity score						<0.001
None	22.6(177)	4.2(38)	1.9(15)	1.5(4)	2.3(5)	
Occasional	33.2(260)	26.6(242)	12.8(99)	7.5(20)	10.7(23)	
Light	14.6(114)	24.2(220)	20.3(157)	19.5(52)	21.9(47)	

Moderate	8.2(64)	12.8(116)	24.1(187)	21.7(58)	27.4(59)	
moderately vigorous	11.5(90)	18.9(172)	20.6(160)	22.5(60)	18.1(39)	
Vigorous	9.8(77)	13.3(121)	20.3(157)	27.3(73)	19.5(42)	
Walking pace						<0.001
Slow	20.8(166)	8.7(80)	7.4(58)	6.3(17)	8.9(19)	
Steady average	57.1(456)	65.1(596)	68.5(535)	66.9(180)	69.6(149)	
Brisk/fast	22.1(176)	26.2(240)	24.1(188)	26.8(72)	21.5(46)	
Miles walked/week[§]	3.9	6.9	9.7	10.6	10.1	<0.001
Prevalent diabetes	11.8(95)	11.3(104)	9(71)	7(19)	8.8(19)	0.091
BMI (kg/m^2)[†]	27.01	26.61	26.69	26.60	26.87	0.274
Waist circumference (cm)[†]	97.62	96.25	96.39	95.94	96.78	0. 051
Plasma vitamin C (µmol/L)[§]	22.71	23.31	23.15	21.76	19.26	0.052
Total Cholesterol (mMol/L)	6.03	6.10	6.07	6.12	5.95	0.892
HDL-Cholesterol	1.34	1.33	1.35	1.36	1.32	0.697

(mMol/L)						
Triglycerides (mMol/L)[‡§]	1.60	1.62	1.60	1.61	1.50	0.250
Systolic blood pressure (mmHg)[†‡]	150.07	150.51	149.88	147.82	149.38	0.297
Diastolic blood pressure (mmHg)[†‡]	85.49	86.16	85.69	85.40	85.09	0.558
Blood pressure lowering medication %(n)	28.2(224)	28.6(260)	26.2(203)	26.3(70)	24.9(52)	0.674
$FEV_{1,}$ (L)[‖]	2.21	2.30	2.29	2.31	2.30	0.016
Heart Rate (beats/minute)	66.14	66.31	65.42	64.70	64.10	0.007
Atrial fibrillation %(n)	2.5(20)	2.6(24)	2.9(23)	2.6(7)	1.9(4)	0.931
Left ventricular hypertrophy %(n)	7.7(62)	6.6(61)	6.6(52)	8.6(23)	7.4(16)	0.754
C-reactive protein, (mg/L)[§]	1.78	1.51	1.64	1.44	1.74	0.248
Von Willebrand Factor	137.	136.98	137.56	134.58	132.27	0.129

(IU/dL)						
D-dimer (ng/mL)[§]	81.75	76.85	79.92	74.17	69.39	0.016
NT-ProBNP (pg/mL)[§]	85.66	82.52	91.00	79.78	77.62	0.538

[*] P(trend) tested with linear regression for continuous variables and chi squared for categorical variables

[†]adjusted for inter-observer variation

[‡]adjusted for time of day

[§] geometric mean

[‖] adjusted for inter-observer variation and height squared.

Table 2 Association between (i) total physical activity with onset of stroke, up to June 2010.

1. Total leisure time physical activity	None	Occasional	Light	Moderate	Moderately vigorous & vigorous	Total	P (trend)
Participants(n)	269	690	569	475	992	2995	
Person years	2279	6451	5570	4768	9938	29,001	
Stroke events rates/ 1000 (n)	7.9(18)	8.1(52)	7.5(42)	5.7(27)	5.6 (56)	6.7(195)	
HR (95% CI)*							
Model 1	1.0	1.08(0.63,1.85)	0.99(0.57,1.71)	0.81(0.44,1.48)	0.79(0.46,1.34)		0.092
Model 2	1.0	1.05(0.61,1.82)	0.93(0.53,1.63)	0.80(0.43,1.47)	0.77(0.45,1.34)		0.100

*From Cox regression models of physical activity level and all stroke

Model 1 = age+ region;

Model 2 = model 1+alcohol intake (none/occasional, 1-15 units/week, >15 units/week)+smoking history (never-smoker, ex-smoker, current smoker)+social class (non-manual, manual and armed forces) + total cholesterol+ HDLc + $\log_e$ (triglycerides) + SBP+ taking blood pressure

lowering medication+ BMI

Table 3 Association between distance walked /week with onset of stroke, up to June 2010.

2. Distance walked/week	0-3 miles/ week	4-7 miles/ week	8-14 miles/ week	>15 miles/ week	Total	P (trend)
Participants(n)	697	805	787	526	2815	
Person years	6508	7868	7714	5264	27,354	
Stroke events rates/ 1000 (n)	7.4(48)	6.6(52)	7.8(60)	4.9(26)	6.8(186)	
HR (95% CI)*						
Model 1	1.0	0.92(0.62,1.37)	1.12(0.76,1.64)	0.73(0.45,1.19)		0.505
Model 2	1.0	0.89(0.60,1.33)	1.08(0.73,1.59)	0.70(0.43,1.15)		0.403

*From Cox regression models of physical activity level and all stroke

Model 1 = age+ region;

Model 2 = model 1+alcohol intake (none/occasional, 1-15 units/week, >15 units/week)+smoking history (never-smoker, ex-smoker, current smoker)+social class (non-manual, manual and armed forces) + total cholesterol+ HDLc + $\log_e$ (triglycerides) + SBP+ taking blood pressure lowering medication+ BMI

Table 4 Association between time spent walking /week with onset of stroke, up to June 2010.

3. Time spent walking/week	0-3 hours	4-7 hours	8-14 hours	15-21 hours	>=22 hours	Total	P (trend)
Participants (n)	633	747	612	210	183	2385	
Person years	6024	7341	6024	2095	1060	23,196	
Stroke events rate/1000 (n)	8.0(48)	7.7(56)	5.5(33)	5.3(11)	2.7(5)	6.6(153)	
HR (95% CI)*							
Model 1	1.0	0.89(0.60,1.31)	0.63(0.40,1.00)	0.68(0.35,1.32)	0.36(0.14,0.91)		0.006
Model 2	1.0	0.88(0.60,1.31)	0.65(0.41,1.02)	0.69(0.35,1.34)	0.34(0.13,0.87)		0.006
Model 3	1.0	0.90(0.61,1.33)	0.66(0.42,1.04)	0.70(0.36,1.36)	0.35(0.14,0.88)		0.008
Model 4	1.0	0.89(0.60,1.33)	0.66(0.42,1.04)	0.70(0.36,1.36)	0.35(0.14,0.88)		0.007
Model 5	1.0	0.91(0.61,1.34)	0.66(0.42,1.04)	0.70(0.36,1.36)	0.35(0.14,0.89)		0.008

*From Cox regression models of physical activity level and all stroke

Model 1 = age+ region;

Model 2 = model 1+alcohol intake (none/occasional, 1-15 units/week, >15 units/week)+smoking history (never-smoker, ex-smoker, current

smoker)+social class (non-manual, manual and armed forces) + total cholesterol+ HDLc + $\log_e$ (triglycerides) + SBP+ taking blood pressure lowering medication+ BMI

Model 3= model 2+ walking pace

Model 4= model 3+ FEV_1

Model 5= model 3+ $\log_e$ (C-reactive protein) + $\log_e$ (d-dimer) + $\log_e$ (NT-ProBNP)

Table 5 Association between usual walking pace week with onset of stroke, up to June 2010.

4. Walking pace	**Slow**	**>=Steady average**	**Total**	**P (trend)**
Participants (n)	319	2464	2783	
Person years	2626	2441	27067	
Stroke events rate/ 1000 (n)	11.8(31)	6.1(150)	6.7(181)	
HR (95% CI)*				
Model 1	1.00	0.62(0.42,0.92)		0.017
Model 2	1.00	0.66(0.44,1.00)		0.038
Model 3	1.00	0.67(0.44,1.02)		0.063
Model 4	1.00	0.67(0.43,1.04)		0.077

*From Cox regression models of physical activity level and all stroke

Model 1 = age+ region;

Model 2 = model 1+alcohol intake (none/occasional, 1-15 units/week, >15 units/week)+smoking history (never-smoker, ex-smoker, current smoker)+social class (non-manual, manual and armed forces) + total cholesterol+ HDLc + $\log_e$ (triglycerides) + SBP+ taking blood pressure

lowering medication+ BMI

Model 3= model 2 + waking distance

Model 4= model 2 + walking time