Association between features of the insulin resistance syndrome and Alzheimer's disease independently of apolipoprotein E4 phenotype: cross sectional population based study

Johanna Kuusisto, Keijo Koivisto, Leena Mykkänen, Eeva-Liisa Helkala, Matti Vanhanen, Tuomo Hänninen, Kari Kervinen,Y Antero Kesäniemi, Paavo J Riekkinen, Markku Laakso

Abstract

Objective: To determine the association between features of the insulin resistance syndrome and Alzheimer's disease.
Design: Cross sectional population based study.
Subjects: 980 people aged 69 to 78 (349 men, 631 women).
Setting: Population of Kuopio, eastern Finland.
Main outcome measures: Presence of features of the insulin resistance syndrome and diagnosis of Alzheimer's disease by detailed neurological and neuropsychological evaluation.
Results: 46 (4.7%) subjects were classified as having probable or possible Alzheimer's disease. In univariate analyses, apolipoprotein E4 phenotype (odds ratio; 95% confidence interval 3.24: 1.77 to 5.92), age (1.16; 1.05 to 1.29), low level of education (0.82; 0.72 to 0.93), low total cholesterol concentration (0.77; 0.59 to 1.00), high systolic blood pressure (1.01; 1.00 to 1.03), high fasting and 2 hour plasma glucose concentrations (1.11; 1.01 to 1.23 and 1.08; 1.03 to 1.13, respectively), high fasting and 2 hour insulin concentrations (1.05; 1.02 to 1.08 and 1.003; 1.00 to 1.01, respectively), and abnormal glucose tolerance (1.86; 1.23 to 2.80) were significantly associated with Alzheimer's disease. In multivariate analysis including apolipoprotein E4 phenotype, age, education, systolic blood pressure, total cholesterol concentration, fasting glucose concentration, and insulin concentration, apolipoprotein E4 phenotype, age, education, total cholesterol, and insulin were significantly associated with Alzheimer's disease. In 532 non-diabetic subjects without the e4 allele hyperinsulinaemia was associated with an increased risk for Alzheimer's disease (prevalence of disease 7.5% *v* 1.4% in normoinsulinaemic subjects, P = 0.0004). In contrast, in the 228 with the e4 allele hyperinsulinaemia had no effect on the risk of disease (7.0% *v* 7.1%, respectively).
Conclusion: Features of the insulin resistance syndrome are associated with Alzheimer's disease independently of apolipoprotein E4 phenotype.

Introduction

The importance of apolipoprotein E4 phenotype as a risk factor for late onset Alzheimer's disease has recently been well established.[1,2] Our previous study indicated that the prevalence of Alzheimer's disease in an elderly Finnish cohort was 2.9% in subjects with no e4 alleles, 7.6% in subjects with one e4 allele, and 21.4% in subjects with two e4 alleles.[2] Yet, apolipoprotein E4 phenotype is neither necessary nor sufficient for the expression of Alzheimer's disease.[2,3] Evidently, other genetic or environmental factors contribute to the aetiology and pathogenesis of the disease.

As Alzheimer's disease is common, its risk factors should also be prevalent. Adverse changes in cardiovascular risk factors are common in Western countries, particularly in elderly subjects. Information on the relation of other cardiovascular risk factors apart from apolipoprotein E4 phenotype with the risk for Alzheimer's disease, however, is limited.[4,5] The insulin resistance syndrome—characterised by insulin resistance and concomitant hyperinsulinaemia, obesity, especially central obesity, high triglyceride concentration, low high density lipoprotein cholesterol concentration, hypertension, impaired glucose tolerance, and diabetes—has not been thoroughly evaluated as a risk factor for Alzheimer's disease. There are few previous reports on small numbers of patients suggesting that high glucose, insulin,[6] and triglyceride concentrations,[5] all features of the insulin resistance syndrome, are associated with Alzheimer's disease, but there are also studies contradicting these associations.[7,8] Lately, two population based studies have also shoiwn an association between Alzheimer's disease and diabetes[9] and between Alzheimer's disease and atherosclerosis.[10]. In our study we investigated the association of cardiovascular risk factors with Alzheimer's disease in a large randomly selected elderly population from eastern Finland.

Subjects and methods

Subjects

The subjects for this study were selected from a population based study investigating risk factors and prevalence of atherosclerotic vascular disease in elderly people. The baseline study was conducted in Kuopio, eastern Finland, in 1986-8, and it included 1300 subjects aged 65-74 years who were randomly selected from the inhabitants of the town of Kuopio.[11] The follow up study was performed in 1990-1, an average of 3.5 years after the baseline study. From 1192 subjects still alive, 980 eventually participated in the follow up examination that included the screening for dementia.[2]

Laboratory tests

The cardiovascular risk factors used in this study were measured at the follow up examination of the study, about 2-3 weeks before the screening for dementia. All cardiovascular risk factors, including glucose tolerance and insulin concentrations, however, were also

Department of Medicine, Kuopio University Hospital, PO Box 1777, FIN-70211 Kuopio, Finland
Johanna Kuusisto, *lecturer in medicine*
Leena Mykkänen, *consultant physician*
Markku Laakso, *professor*
Department of Neurology, Kuopio University Hospital
Keijo Koivisto, *consultant physician*
Eeva-Liisa Helkala, *psychologist*
Matti Vanhanen, *psychologist*
Tuomo Hänninen, *psychologist*
Paavo J Riekkinen, *professor*
Department of Internal Medicine, Oulu University Hospital and Biocenter Oulu, University of Oulu, Oulu, Finland
Kari Kervinen, *consultant physician*
Y Antero Kesäniemi, *professor*
Correspondence to: Professor Laakso

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measured at baseline, 3.5 years before screening for dementia, and the association of these previously measured variables with Alzheimer's disease was also evaluated.

Glucose tolerance—All subjects, except for those receiving insulin, underwent a 75 g oral 2 hour glucose tolerance test after a 12 hour fast. World Health Organisation diagnostic criteria for normal glucose tolerance, impaired glucose tolerance, and diabetes mellitus were used in the classification of glucose tolerance group.[12]

Determination of apolipoprotein E phenotypes—The apolipoprotein E phenotype was determined from serum samples with isoelectric focusing and immunoblotting techniques by using commercial antibodies.[13 14]

Other laboratory methods—Plasma glucose concentration was determined by the glucose oxidase method (Glucose Auto and Stat HGA-1120 analyser, Daiichi, Kyoto, Japan). Plasma insulin was determined from samples stored at −70°C by a double antibody solid phase radioimmunoassay (Phadeseph Insulin RIA 100, Pharmacia Diagnostica AB, Uppsala Sweden).[15] Concentrations of glycated haemoglobin A_{1c}, total and high density lipoprotein cholesterol, and total triglyceride were determined as previously described in detail.[16]

Diagnosis of coronary heart disease and stroke events—Both at baseline and follow up a conventional 12 lead resting electrocardiogram was recorded, and the classification of the tracings was made according to the Minnesota code.[17] We used WHO criteria modified by the Finnish MONICA (monitoring trends and determinants in cardiovascular disease) Study Group for verified definite and possible myocardial infarction based on symptoms of chest pain, electrocardiographic changes, and enzyme determinations in ascertaining previous myocardial infarction.[18 19] WHO criteria for definite and possible stroke were used in the ascertainment of previous stroke, which was defined as a clinical syndrome consisting of neurological deficits persisting over 24 hours and observed by a neurologist without other diseases explaining the symptoms.[20] Thromboembolic and haemorrhagic strokes, but not subarachnoidal haemorrhage, were included in the diagnosis of stroke.

Diagnosis of dementia

The diagnosis of dementia was based on a three phase programme.

Phase 1—All study subjects (n = 980) were evaluated by neuropsychological tests. Phase 1 involved a screening battery of five neuropsychological tests aimed at identifying patients who were potentially demented. The cognitive test battery included the minimental state examination, Russell's adaptation of the visual reproduction test, the trail making test, the verbal fluency test, and the Buschke selective reminding test. A detailed description of these screening tests has been recently published.[21]

Phase 2—Subjects scoring ≤1 SD below the mean score in the minimental status examinations adjusted for education or below the cut off point score (≤1 SD below the mean score in normal healthy elderly subjects of similar age), or both, in three of four other screening tests were selected for an extensive neuropsychological and neurological examination to confirm the possibility of dementia (n = 232). The detailed neuropsychological test battery included 12 tests.[22 23] The diagnosis of dementia was based on the criteria of *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R).[24]

Phase 3—All subjects with possible dementia (n = 66) were admitted to the department of neurology, Kuopio University Hospital, for further studies. The final diagnosis and classification of dementia was set by the board of two neuropsychologists and two neurologists. All those for whom the diagnosis was confirmed underwent computed tomography. The classification of dementia was as follows: probable or possible Alzheimer's disease; vascular dementia; and secondary dementia including other causes of dementia. The diagnosis of Alzheimer's disease was based on the criteria of the National Institute of Neurological Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association [25] and the diagnosis of multi-infarct dementia on DSM-III-R criteria.[24]

Statistical methods

Data analyses were conducted with the SPSSX and SPSS/PC+ programs. Data are given as mean (SE) or percentages. Student's two tailed *t* test for independent samples or χ^2 test were used in the assessment of the differences between the groups when appropriate. Univariate and multiple logistic regression analyses based on the maximum likelihood method were used to investigate the association of cardiovascular risk factors with the prevalence of Alzheimer's disease. Odds ratios (95% confidence intervals) were calculated by logistic regression analysis.

Approval of ethics committee

This study was approved by the ethics committee of the Kuopio University Hospital. All study subjects gave informed consent.

Results

Altogether 980 subjects completed the follow up examination and neuropsychological screening for dementia (phase 1). Of these, 19 were diagnosed with dementia of non-Alzheimer type (nine with vascular dementia and 10 with secondary dementia) and excluded, leaving 961 subjects (762 non-diabetic and 199 diabetic subjects) in the study. Of these, 46 were diagnosed with Alzheimer's disease. In 38 of these 46 patients the diagnosis was made in our study.

Table 1 shows the levels of cardiovascular risk factors measured 2-3 weeks before the screening for dementia in study subjects with and without Alzheimer's disease. In addition to having increased prevalence of apolipoprotein E4 phenotype, patients with Alzheimer's disease were older and had fewer years of education, higher systolic blood pressure, higher fasting and 2 hour glucose concentrations, higher fasting and 2 hour insulin concentrations, and increased prevalence of diabetes and impaired glucose tolerance. Of the 46 subjects with Alzheimer's disease, only 13 had normal glucose tolerance. In non-diabetic subjects, the results of the aforementioned analyses were the same except that diastolic blood pressure was significantly higher and hypertension was more prevalent in subjects with Alzheimer's disease compared with those without it (data not shown).

Table 2 shows risk factors for Alzheimer's disease by univariate logistic regression analysis in all study subjects. In addition to apolipoprotein E4 phenotype, age, low level of education, the presence of abnormal glucose tolerance (diabetes or impaired glucose tolerance), high systolic blood pressure, low total cholesterol concentration, high fasting and 2 hour glucose concentrations, and high fasting and 2 hour insulin concentrations were associated with an increased risk for Alzheimer's disease. In non-diabetic subjects, in addition to these variables, hypertension and high diastolic blood pressure were also associated with Alzheimer's disease (data not shown).

Table 3 shows the results of the multiple logistic regression analysis on risk factors for Alzheimer's disease in all study subjects. Variables associated with the risk for Alzheimer's disease in univariate analyses were included in the model. Age, low level of education, low total cholesterol concentration, apolipoprotein E4 phenotype, and high fasting insulin concentration were independently associated with the risk for Alzheimer's disease. In non-diabetic subjects, low level of education, high systolic blood pressure, low total cholesterol concentration, apolipoprotein E4 phenotype, and high fasting insulin concentration were independently associated with the risk of Alzheimer's disease.

The association between Alzheimer's disease and baseline cardiovascular risk factors measured 3.5 years before the screening for dementia were also studied by logistic regression analyses. In univariate analysis, the same variables which were associated with Alzheimer's disease at follow up were also associated with Alzheimer's disease when we used parameters measured at baseline (data not shown). In multivariate analysis, age (1.15; 1.03 to 1.29; P = 0.013), low level of education (0.83; 0.73 to 0.95; P = 0.005), low cholesterol concentration (0.67; 0.50 to 0.87; P = 0.004), apolipoprotein E4 phenotype (3.53; 1.86 to 6.68; P = 0.0001), and high insulin concentration (1.03; 1.00 to 1.05; P = 0.040) but not systolic blood pressure (1.01; 0.73 to 1.02; P = 0.25) or fasting plasma glucose (1.09; 0.74 to 1.23; P = 0.46) were significantly associated with the risk for Alzheimer's disease.

Finally, we investigated the risk of Alzheimer's disease in hyperinsulinaemic subjects with and without the e4 allele. As insulin concentration is a good marker for insulin resistance in non-diabetic subjects but not in those with diabetes[26] we analysed the association between Alzheimer's disease and hyperinsulinaemia in non-diabetic subjects. Hyperinsulinaemia was defined as the highest insulin quintile (>89.4 pmol/l) in this subgroup. In subjects without the e4 allele (n = 532) hyperinsulinaemia was associated with an increased risk for Alzheimer's disease (the prevalence of Alzheimer's disease in hyperinsulinaemic versus normoinsulinaemic subjects 7.5% and 1.4%, respectively, P = 0.0004). In contrast, in subjects with the e4 allele (n = 228) hyperinsulinaemia had no effect on the risk of Alzheimer's disease (7.0% and 7.1%, respectively, P = 0.65).

Discussion

The results of the present study indicate that cardiovascular risk factors related to the insulin

Table 1 Characterics of study subjects with and without Alzheimer's disease. Values are means (SE) unless stated otherwise

Characteristic	No Alzheimer's disease (n=915)	Alzheimer's disease (n=46)
Sex (M/F)	324/591	14/32
Age (years)	72.9 (0.1)	74.1 (0.4)**
Education (years)	6.8 (0.1)	5.1 (0.6)**
No (%) of smokers	61 (6.7)	3 (6.7)
No (%) of alcohol users	163 (17.8)	8 (17.4)
No (%) with hypertension†	507 (55.4)	29 (63.8)
No (%) with myocardial infarction	129 (14.1)	8 (17.4)
No (%) with stroke	34 (3.7)	1 (2.2)
No (%) with diabetes	182 (19.9)	15 (32.6)**
No (%) with impaired glucose tolerance	182 (19.9)	17 (37.0)***
Body mass index (kg/m^2)	27.1 (0.1)	27.4 (0.8)
Waist:hip ratio	0.94 (0.00)	0.95 (0.01)
Systolic blood pressure (mm Hg)‡	155 (1)	162 (4)*
Diastolic blood pressure (mm Hg)‡	82 (0)	84 (2)
Total cholesterol (mmol/l)	6.5 (0.0)	6.2 (0.2)
High density lipoprotein cholesterol (mmol/l)	1.36 (0.01)	1.30 (0.06)
Triglycerides (mmol/l)	1.68 (0.03)	1.85 (0.14)
No (%) with apolipoprotein E4 phenotype (%)	279 (30.5)	27 (58.7)***
Fasting plasma glucose (mmol/l)	6.2 (0.1)	6.9 (0.4)*
Two hour plasma glucose (mmol/l)	8.3 (0.1)	10.6 (0.9)**
Haemoglobin A_{1c}	6.0 (0.0)	6.3 (0.2)
Fasting insulin (pmol/l)	74.8 (1.5)	99.3 (9.4)***
Two hour insulin (pmol/l)	500.9 (14.8)	682.3 (108.8)*

*P<0.05, **P<0.01, ***P<0.001.
†Systolic blood pressure ⩾160 mm Hg, diastolic blood pressure ⩾95 mm Hg, or drug treatment for hypertension.
‡ Measured twice on right arm in supine position after 5 minutes' rest. Second reading used in analyses.

Table 2 Association of characteristics with Alzheimer's disease in univariate logistic regression analysis

Characteristic	Odds ratio (95% CI)	P value
Sex	1.25 (0.66 to 2.36)	0.49
Age	1.16 (1.05 to 1.29)	0.005
Education	0.82 (0.72 to 0.93)	0.002
Smoking	0.88 (0.61 to 1.25)	0.47
Alcohol use	0.97 (0.45 to 2.11)	0.94
Hypertension	1.37 (0.75 to 2.52)	0.31
Myocardial infarction	1.28 (0.59 to 2.79)	0.53
Stroke	0.58 (0.08 to 4.30)	0.59
Abnormal glucose tolerance	1.86 (1.23 to 2.80)	0.003
Body mass index	1.02 (0.95 to 1.09)	0.67
Waist:hip ratio	2.96 (0.08 to 108.08)	0.56
Systolic blood pressure	1.01 (1.00 to 1.03)	0.039
Diastolic blood pressure	1.03 (1.00 to 1.05	0.09
Total cholesterol	0.77 (0.59 to 1.00)	0.049
High density lipoprotein cholesterol	0.60 (0.25 to 1.45)	0.26
Triglycerides	1.13 (0.91 to 1.41)	0.28
Apolipoprotein E4 phenotype	3.24 (1.77 to 5.92)	0.0001
Fasting plasma glucose	1.11 (1.01 to 1.23)	0.031
Two hour plasma glucose	1.08 (1.03 to 1.13)	0.002
Haemoglobin A_{1C}	1.14 (0.95 to 1.36)	0.16
Fasting insulin	1.05 (1.02 to 1.08)	0.0005
Two hour insulin	1.003 (1.00 to 1.01)	0.013

Table 3 Multiple logistic regression analysis on risk factors for Alzheimer's disease

Character	Odds ratio (95% CI)	P value
Age	1.12 (1.01 to 1.25)	0.039
Education	0.83 (0.73 to 0.95)	0.006
Systolic blood pressure	1.01 (1.00 to 1.02)	0.129
Total cholesterol	0.69 (0.52 to 0.92)	0.011
Apolipoprotein E4 phenotype	3.60 (1.91 to 6.79)	0.0001
Fasting plasma glucose	1.10 (0.93 to 1.24)	0.095
Fasting insulin	1.04 (1.01 to 1.08)	0.018

resistance syndrome are associated with the risk of Alzheimer's disease independently of the apolipoprotein E4 phenotype. So far as we know, our study is the first to show that the insulin resistance syndrome is associated with Alzheimer's disease. This association was shown in a randomly selected large population sample in which most of the cases of Alzheimer's disease were newly detected. Essentially the same risk factors for Alzheimer's disease were detected when cardiovascular risk factors measured 3.5 years before the screening for dementia were used in the analyses instead of those measured 2-3 weeks before the screening. Our study design minimises the possibility that advanced dementia interfering with cardiovascular risk factors might bias the results of the study.

Why have previous studies not been able to show an association between cardiovascular risk factors related to insulin resistance and Alzheimer's disease? Most studies have included patients with established Alzheimer's disease. Advanced Alzheimer's disease is a catabolic state with low blood pressure and low total cholesterol and low blood glucose concentrations.[8] This catabolic state may interfere with the insulin resistance syndrome characterised by opposite features and bias risk factor analysis.

How might the insulin resistance syndrome increase the risk for Alzheimer's disease? On the basis of the present results definitive answers cannot be given, but other studies suggest interesting connections between glucose and insulin metabolism and brain function. Diabetes is associated with dementia,[9] and in our study diabetes increased the risk for Alzheimer's disease. Consequently, hyperglycaemia might be a risk factor for Alzheimer's disease. Indeed, according to a recent report, advanced glycation end products, which accumulate in tissues as a function of time and blood glucose concentration[27] are found in amyloid plaques of Alzheimer's disease.[28] Thus, hyperglycaemia associated with an increased production of advanced glycation end products may contribute to the formation of amyloid plaques in Alzheimer's disease.

Although hyperglycaemia might be one factor explaining the association between the insulin resistance syndrome and Alzheimer's disease, it is probably not the only one. In our study, fasting insulin, a key feature of the insulin resistance syndrome and also an integral part of impaired glucose tolerance, was significantly associated with Alzheimer's disease. In non-diabetic subjects, hyperinsulinaemia (fasting insulin >89.4 pmol/l) was, in fact, associated with as high a risk of Alzheimer's disease as the presence of apolipoprotein E4 phenotype. In our previous study, hyperinsulinaemic hypertension was also associated with poor cognitive function.[29] Insulin is transported to cerebrospinal fluid and also synthesised in the brain, where it acts as a neuromodulator regulating energy balance.[30 31] Hyperinsulinaemia might interfere with brain function making it more vulnerable to Alzheimer's disease or contribute to amyloid plaque formation. It is also possible, however, that other aspects of the insulin resistance syndrome, such as accelerated atherosclerosis,[10 32] are responsible for the association between the insulin resistance syndrome and Alzheimer's disease.

In patients with Alzheimer's disease, the question of validity of informed consent is appropriate. In our study, 38 of the 46 patients with Alzheimer's disease were diagnosed with dementia during our study. The eight patients with previously known Alzheimer's disease were relatively mildly affected and could participate in the study by themselves.

In conclusion, features of the insulin resistance syndrome are associated with Alzheimer's disease, independently of the apolipoprotein E4 phenotype. Alzheimer's disease may resemble coronary heart disease, in which several factors contribute to the risk for the disease. Even more importantly, as the insulin resistance syndrome is at least in part preventable by modification of life style, Alzheimer's disease might also be preventable, at least in some cases, thus opening new areas for researchers.

Key messages

- Apolipoprotein E4 phenotype is a risk factor for Alzheimer's disease
- Other risk factors for Alzheimer's disease are not well documented in previous studies
- In this study, hyperinsulinaemia and other features of the insulin resistance syndrome were associated with Alzheimer's disease
- Insulin resistance is affected by modifications in lifestyle, so the risk of Alzheimer's disease might be reducible by the same measures

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Conflict of interest: None.

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Development and evaluation of evidence based risk assessment tool (STRATIFY) to predict which elderly inpatients will fall: case-control and cohort studies

D Oliver, M Britton, P Seed, F C Martin, A H Hopper

Abstract

Objectives: To identify clinical characteristics of elderly inpatients that predict their chance of falling (phase 1) and to use these characteristics to derive a risk assessment tool and to evaluate its power in predicting falls (phases 2 and 3).
Design: Phase 1: a prospective case-control study. Phases 2 and 3: prospective evaluations of the derived risk assessment tool in predicting falls in two cohorts.
Setting: Elderly care units of St Thomas's Hospital (phase 1 and 2) and Kent and Canterbury Hospital (phase 3).
Subjects: Elderly hospital inpatients (aged ≥65 years): 116 cases and 116 controls in phase 1, 217 patients in phase 2, and 331 in phase 3.
Main outcome measures: 21 separate clinical characteristics were assessed in phase 1, including the abbreviated mental test score, modified Barthel index, a transfer and mobility score obtained by combining the transfer and mobility sections of the Barthel index, and several nursing judgments.
Results: In phase 1 five factors were independently associated with a higher risk of falls: fall as a presenting complaint (odds ratio 4.64 (95% confidence interval 2.59 to 8.33); a transfer and mobility score of 3 or 4 (2.10 (1.22 to 3.61)); and primary nurses' judgment that a patient was agitated (20.9 (9.62 to 45.62)), needed frequent toileting (2.48 (1.08 to 5.70)), and was visually impaired (3.56 (1.26 to 10.05)). A risk assessment score (range 0-5) was derived by scoring one point for each of these five factors. In phases 2 and 3 a risk assessment score >2 was used to define high risk: the sensitivity and specificity of the score to predict falls during the following week was 93% and 88% respectively in phase 2 and 92% and 68% respectively in phase 3.
Conclusion: This simple risk assessment tool predicted with clinically useful sensitivity and specificity a high percentage of falls among elderly hospital inpatients.

Introduction

Falls are common among elderly hospital inpatients.[1 2] For the patient, consequences may include fracture,[3 4] fear of falling,[5] anxiety and depression,[6] and loss of confidence,[7] all of which lead to greater disability. Falls by inpatients are associated with increased duration of stay in hospital and a greater chance of unplanned readmission or of discharge to residential or nursing home care.[8]

Successful rehabilitation to minimise long term disability of elderly people requires that staff aim to reduce patients' dependency and to increase their autonomy during recovery from acute illness when it is associated with disability. The occurrence of some falls is an unwelcome but probably inevitable consequence of encouraging patients to regain mobility early after acute illness. None the less, there may be simple measures that could reduce the incidence of falls[2 9] without the need for physical restraints, sedation, excessive supervision, or other measures that undermine a patient's dignity and independence.

A strategy which has proved successful in the prevention of pressure sores[10] is to select patients at high risk and target prevention strategies. Various clinical characteristics (over 400 in total on systematic review[11]) have been shown to be associated with an increased incidence of falls occurring at home or outdoors. Examples include use of particular drugs, muscle weakness, unstable gait, postural hypotension, and

Department of Elderly Care (Division of Medicine), United Medical and Dental Schools, St Thomas's Hospital, London SE1 7EH
D Oliver, *senior registrar*
M Britton, *senior registrar*
F C Martin, *consultant physician*
A H Hopper, *consultant physician*
Department of Statistics (Division of Public Health Sciences), United Medical and Dental Schools, St Thomas's Hospital
P Seed, *lecturer*
Correspondence to: Dr Oliver

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