Neuropathological correlates of falling in the CC75C population-based sample of the older old

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Abstract

Background

Previous imaging studies have suggested links between brain pathologies and factors that are associated with falls such as gait, balance and daily function. Possible neuropathological correlates of older people's falls have been suggested based on brain imaging studies, but to date none have been examined in brain tissue.

Methods

Falls data collected from repeated surveys of a population-based cohort of individuals aged at least 75 years old at baseline were related to neuropathological data collected from post-mortem examination of the study's associated brain donor collection (n=212).

Results

Amongst people without dementia, most cerebrovascular neuropathological features examined, particularly white matter pallor, microinfarcts and microscopic atherosclerosis, were increasingly common across the sub-groups categorised by no reports of falling, only one or at least two reports of falling. The overall burden of pathology was greater in those with dementia, but only microinfarcts showed a similar increase with respect to reported falling status.

Conclusions

Subclinical pathologies sharing a common vascular origin are associated with increased falling amongst people with no dementia, as are microinfarcts in those with dementia. Although further research is needed to address the mechanisms of falls and their neuropathological correlates, the findings from the current study would suggest that if cerebrovascular disease prevention reduces vascular neuropathology changes

this may have direct benefits in reducing falls amongst older people with or without

dementia.

Abstract: 222 words

Background

Falling is common in old age, particularly in older old age and in individuals with dementia (1, 2). Falls amongst older people are a growing public health concern as demographic trends forecast an increasingly ageing population (3). The aetiology of falls is multi-factorial and the neuropathological contributions to factors associated with mobility impairments such as gait changes and poor balance are not clear (4).

Various imaging studies have suggested links between subclinical brain pathologies, such as white matter changes, brain atrophy and ischaemic lesions, and factors that are associated with falls in the older population, such as gait disorders, impaired balance, postural instability and other measures of daily function (5-7).

White matter lesions, seen as hyperintensities on MRI and hypointensities on CT, include a variety of lesion types that may be markers for cerebrovascular disease (8-10). Neuropathologically, these lesions include gliosis, expansion of perivascular spaces, small diffuse infarcts, lacunar infarcts, axonal loss and demyelination (11).

Total volume of white matter abnormalities seen on MRI has been associated with gait disturbance (5, 12-18), balance impairments (5, 13-15, 19, 20), increased tendency to fall (17, 18, 21, 22) and hip fracture (23). While some studies have demonstrated an association between decreased mobility and lesions located in deep white matter (24), others have found this more strongly associated with periventricular lesions (25, 26), and a recent study suggested that both locations were independently associated with gait impairments and falls(27)

Brain atrophy, as evidenced by ventricular enlargement (20, 21, 25, 28) and grey matter volumes measured on MRI (29), has been associated with gait disturbances

and balance impairments. This association may be independent from white matter lesions(28, 29).

Small subcortical infarcts, lacunes and ischaemic lesions in the basal ganglia have also been associated with decreased mobility (21, 24, 30, 31). While neuroimaging studies easily detect lacunes and small infarcts (>3mm) in white matter, microinfarcts in grey matter are not so easily detected (32) and may be better analysed in post mortem brain tissue. Microinfarcts in grey matter at autopsy have been associated with cognitive decline (32, 33) but, to our knowledge, have not been examined in brain tissue with respect to falls in older persons.

In the current study, we sought to explore the relationship between falls data collected from repeated surveys of a population-based cohort aged at least 75 years at baseline and findings from post-mortem examination of the study's associated brain donor collection. In addition to the possible neuropathological correlates suggested by neuroimaging studies, we investigated the effects of tau reactive tangles in the substantia nigra which have previously been associated with gait disorders (34, 35).

Methods

The cohort sample: recruitment, assessments and brain donation
The Cambridge City over-75s Cohort (CC75C) study is a longitudinal population-based study of cognition and function in older old age with an associated brain donation programme for examination of neuropathological correlates of changes with ageing (www.cc75c.group.cam.ac.uk; (36, 37)). It began in the mid-1980s with a survey of dementia prevalence amongst men and women aged at least 75 recruited from six

general practices to provide a socially representative sample of all older residents of Cambridge, UK. The baseline response rate was 95% (n=2166) and over the 23 years of follow-up to date, with repeated interview waves every few years, the main cause of attrition has been mortality. In the initial phase of the study, the full-sample surveys were followed by intensive examination of sub-samples using the Cambridge Diagnostic Examination for the Elderly (38) (39), a psychiatrist administered assessment that also includes a proxy informant interview. Participants were sampled for intensive CAMDEX interviews (94% participation rate) on the basis of Mini-Mental State Examination (40) (MMSE) scores: all scoring MMSE 0-23, suggesting low to moderate cognitive function, and 1 in 3 with MMSE scores 24-25, suggesting mild or minimal cognitive impairment.

CC75C is one of the three European population-based studies with brain donation programmes that form EClipSE (Epidemiological Clinicopathological Studies in Europe www.eclipsestudy.eu). Approaching participants to raise the possibility of donation to the study's brain collection began shortly after the second full survey, known then as the Cambridge Project for Later Life (CPLL), focussing initially on those who had completed CAMDEX assessments. The recruitment methods and high rates of consent from participants, assent from relatives and successful collection have been previously reported after this initial phase (41). Subsequently participants whose MMSE scores suggested normal to high cognitive function were also recruited to the brain donation programme to ensure the sample would reflect the full population spectrum. Although clinically diagnosed dementia assessments could not be made for the full cohort, the distribution of MMSE scores in the baseline sample closely matches those of the brain donor sample. Besides the in-depth CAMDEX assessments made on many donors, retrospective interviews were sought with relatives at least six months after a donor's death to obtain further information on the period elapsed since a participant was last interviewed until they died.

A consensus diagnosis for dementia status at death for all brain donors was agreed by two clinicians (CB, TD) blinded to neuropathology findings using post-mortem review of all interviews including proxy informant data and death certificates. Dementia status was defined as mild or more severe dementia versus minimal or no dementia. Minimal dementia refers to the CAMDEX category of that name(39), a limited and variable cognitive impairment falling short of a clinical diagnosis of dementia. Dementia status from clinical diagnosis has been described in detail elsewhere(42).

Measures of falling

The CC75C study in later surveys has included a focus on falling in advanced old age (43), but all surveys have collected at least minimal falls data. At baseline and in the early follow-up interviews falls were included in a section on physical health problems in general with questions "What particular difficulties do you have?" and "Have you recently had an illness or condition which prevented you carrying out your normal day-to-day routine?" referring to the previous month. The list of possible disabling conditions that followed always included being "unsteady on your feet"; the listed wording "falls" was changed to "tendency to fall" from Survey 3 (year 7) onwards. A new set of questions specifically on falls was added at Survey 4 (year 10), from which point on interviewees were asked to recall whether they had fallen in the three months before interview and, if so, how many times. An intensive prospective data collection monitored falls for 12 months after Survey 6 (year 17 when the surviving participants were all in their 90s) and information was also gathered on recalled falls in the year before that interview. Falls were explicitly defined for this survey according to the Kellogg International Working Group on Prevention of Falls in Older People (44), but this had not been made specific in earlier surveys. Proxy informants were asked for the same information whenever they provided supplementary survey data, CAMDEX relative interviews or retrospective informant interviews.

All these sources of falls data have been used to classify the brain donor sample into three groups: people for whom no falls nor any tendency to fall was ever reported, people for whom there is only one such report and people with at least two such reports. One person who died shortly after the baseline survey with a positive response to only one fall question was excluded from the analysis as their limited participation could have led to their misclassification. The remaining sample has fall information completed on at least two occasions.

Neuropathology protocol

After death, the brains were removed as soon as possible in the local mortuary. The brains were cut in the sagittal plane. One hemisphere was dissected coronally into approximately one cm slices, macroscopically examined, and the slices were snap frozen at -80°C. Gross atrophy was assessed by eye by an experienced neuropathologist as none, mild, moderate or severe. Measures of the degree of sulcal widening and the degree of ventricular enlargement were recorded as none, mild, moderate or severe separately for frontal, parietal, temporal and occipital cortices and for the hippocampus and cerebellum. Macro-vascular burden was assessed by the number, size and location of visible macro-vascular lesions in any area.

The other half of the brain was dissected coronally into approximately 1 cm slices and formalin fixed for at least six weeks. For diagnostic purposes, blocks for paraffin embedding were taken from: hippocampus (at the level of the lateral geniculate body), entorhinal cortex (at the level of the mamillary body), frontal, temporal, parietal, and occipital lobes, basal ganglia, thalamus, pons, medulla, cerebellum and from two levels of the midbrain. The tissue blocks included cortical and subcortical white matter, deep cerebral white matter and the internal capsule.

Ten micrometer thick sections were stained with haematoxylin and eosin to qualitatively assess neuronal loss, perivascular gliosis, presence of microinfarcts and microvascular appearance in each area. Separate scores were recorded in white and grey matter for V-R space expansion, perivascular gliosis and microinfarcts. Tau and Lewy body pathology was assessed on immunohistochemical preparations using antibodies obtained from the Cambridge Brain Bank Laboratory. Anti-tau antibody (mAb 11.57) was used to immunostain neurofibrillary tangles, neuritic plaques and dystrophic neuirtes. Slides stained with anti-ubiquitin antibody (pAb BR 251; DAKO Z0458, early cases n=174) or anti-α-synuclein (Biomol International SA3400, later cases n=50) and slides stained with haematoxylin and eosin were used to detect Lewy bodies. All immunostained sections were counterstained with Ehrlich's haematoxylin with diaminobenzidine as the chromagen.

Ratings for tau-reactive tangles per section in the substantia nigra were graded as none (no tangles), mild, (one or two) moderate (three to five) and severe (five plus) according to the Consortium to Establish a Registry of Alzheimer's disease (CERAD) (45), protocol. Microinfarcts were scored as present or absent, whereas other microvascular lesions were rated as severe or not severe in all areas. Lewy bodies were assessed by their presence or absence in entorhinal, hippocampal, frontal and temporal cortices and in substantia nigra, nucleus basalis, dorsal raphe nucleus, locus coeruleus and dorsal vagal nucleus. White-matter pallor was rated as severe or not severe in occipital, parietal, frontal, temporal cortices and in deep white matter and the internal capsule. All assessments were performed blind to clinical status by JHX and neuropathologists at Addenbrooke's Hospital, Cambridge UK.

Statistical methods

As of October 2008 the first 224 donations in the CC75C brain donor program had complete neuropathology report data available for analysis (dataset version 3.0). Of these, 11 were excluded from this analysis due to insufficient evidence from interview data to make a clinical diagnosis of dementia. One further participant was excluded as described above because only one response to the falling questions was available. This left 212 individuals in the analysis.

The frequencies of the identified neuropathological variables were examined across dementia and falling status. Ordinal logistic regression by falling status was performed for those neuropathological variables that had sufficient numbers with pathology. The proportional odds assumption was examined via the Brant test (46). In addition, odds ratios were estimated adjusted for age, stroke history and dementia. History of a stroke was obtained from self-report or proxy-report in the surveys or proxy-report in the retrospective informant interviews or as recorded on the death certificate. As differences in risk were observed across the dementia status groups, an interaction between each neuropathological variable and dementia was included in each model enabling the falling risk to be presented by dementia status. A multivariable model was built using a backwards stepwise approach (p=0.1) from those variables with p-values in the adjusted analysis of less than 0.2. Three sensitivity analyses were performed: first to exclude those participants with any Lewy bodies identified in the neuropathology report; second, to minimise the potential for misclassification in falling status by excluding those participants reporting one fall or less whose last fall report was greater than two years prior to death; and third, although results were stratified by dementia status, in addition MMSE score was adjusted for in case differences in cognition in the falling groups affected any neuropathology associations. All analyses were conducted in Stata (Intercooled Version 9.2).

Results

Table 1 describes the characteristics of the sample. There were 150 (71%) women
and 62 (29%) men. Age at death ranged from 81 to 106 years, with a mean (SD) of 91
(4) years, and 53% died with clinical dementia. The mean (SD) length of follow-up was
10 (4) years and the median (IQR) time from last interview until death was 1.6 (0.8-
2.6) years. Around half of the participants (n=105) had retrospective informant
interviews providing falling information up to the time of death. This resulted in the
median time between the last fall reporting and death being less than a month. Most
participants (n=186, 88%) completed a CAMDEX interview prior to death. From all
sources, 77% participants had reports of falling on at least one occasion, and 56% had
reports of falling on two or more occasions. Those reporting repeated falls were more
likely to be female, to have died slightly older, to have dementia and to have reported
a stroke during life.

For most neuropathological variables examined more severe pathology was observed
across the increasing falling groups for those without dementia (table 2). Those with
dementia tended to have more severe pathology, yet the relationship with falling was
generally weak and instead a slight decline in pathological severity was observed
across the increasing falling groups for many variables. The frequencies by dementia
status for atrophy, microscopic atherosclerosis, white matter pallor, Virchow-Robin (V-
R) space expansion, microinfarcts, and neuronal loss in the substantia nigra are also
displayed in Figure 1.

Table 3 displays the ordinal odds ratios (ORs) for predicting falling status.
Arteriolosclerosis was excluded as the proportional odds assumption was violated with
no evidence of an increasing trend. Only white matter pallor, total microinfarcts, and
microinfarcts in the grey matter were associated with falling in the naive univariate

analyses. However, after adjusting for age and self-reported stroke and allowing the OR to vary across dementia status, white matter pallor (overall and in the cortex), microscopic atherosclerosis, V-R space expansion in the white matter, microinfarcts (overall and in the grey matter) were all significantly associated with more frequent falling in those without dementia. In those with dementia only microinfarcts were significantly associated with increased falling status and only moderate/severe tangles were significantly associated with decreased falling status. Less frequent falling was also observed in those with dementia with moderate or severe enlarged ventricles or V-R space expansion in the white matter, but not statistically significantly (p=0.08 and p=0.05). In the multivariable model, microinfarcts remained significantly associated with more frequent falling in those with dementia, although for those without dementia the association decreased and no longer reached statistical significance. White matter pallor and microscopic atherosclerosis also remained independently associated with more frequent falling, but only in those without dementia.

Excluding the 28 participants with Lewy bodies slightly decreased the ORs in the multivariable model for microscopic atherosclerosis and white matter pallor though they are consistent with the confidence intervals of the original model. Excluding the 20 participants reporting at most one fall, but whose last fall report was longer than two years prior to death, had a negligible affect on the results. Lower MMSE score at the last interview before death was also associated with increased falls in both those with and without dementia. However, the neuropathology findings remained unchanged after adjustment for MMSE scores (results not shown).

Discussion

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In this analysis examining post-mortem neuropathology related to falling in old age, we demonstrate an association between falling and increased frequencies of white matter pallor, microinfarcts and microscopic atherosclerosis in individuals without clinical dementia. Although the overall burden of pathology was greater in individuals with dementia, this generally did not vary significantly by reported falling status. Cortical microinfarcts were associated with falling in both the non-demented and to a lesser extent the demented group, and this pattern of association was similar in the different cortical areas investigated.

This study is one of only a handful of population-based studies worldwide that have a long established brain donation collection, one of the longest-running studies of the very old and the first to examine potentially relevant post mortem neuropathology findings in relation to reported falling in a sizeable cohort of the "older old". The strengths of the study include the neuropathological analyses blind to clinical information, the availability of clinical diagnoses of dementia, long period of prospective follow-up in the advanced age-group and data on falling from proxy informants as well as participants for the majority of donors. The statistical approach included multivariable modelling which allowed us to compare the neuropathological features simultaneously. The consistency of results from the three sensitivity analyses - excluding people whose latest interview data were more than two years before death, excluding those with any reported Lewy bodies, and adjusting for MMSE - suggest our findings are robust.

There is inevitably some uncertain classification of the sample into the falling groups. Data were pooled from a variety of sources - participant and proxy informant interviews with questions worded differently over follow-up time. Methodological issues in studies of falls are known to be complex (47): it is common in research and clinical practice to ask about recent falls, despite the obvious questions concerning recall bias,

particularly by people with cognitive impairment (43, 48, 49). The frequency of falls reported during the main surveys for those participating in the brain donation programme and the remaining CC75C survey were found to be similar once adjusted for the number of surveys completed and timing of dropout. Only a minority of the CC75C donors (n=12) have died since our 2002-3 survey, which had falling as a special focus and included a year's prospective falls data collection (43), so our classification of fall status was based largely on reports of recalled falls, using information from proxy informants as well as participants. Moreover the intermittent surveys, intensive for some in the study's initial phase but only every few years later on, may have led to `lost' reports of falling. This might be particularly so for individuals with no retrospective informant interview after death, so any falls at the end of life subsequent to last interviews would be unknown. Recent falling has been highlighted as the most inconsistent health factor from one interview to the next in longitudinal studies of older people (50). Our findings suggesting a trend across fall categories are remarkable given that these limitations of the data on falls would be expected to weaken any associations detected.

Our study used a neuropathological resource generated from the autopsy diagnostic procedure used in the CC75C study. In contrast to other autopsy studies (32, 33), areas of interest were sampled only once. This would lead to a lower chance of sampling pathology of interest and therefore our results are more likely to be an underestimate of any association. Dichotomising the grading of vascular pathology is a coarse measure and again may weaken any association.

Amongst the donors with diagnosed dementia the lack of positive association of any neuropathological features other than microinfarcts with falling is notable, indeed there was suggestion of a negative association for many pathologies. Our analytical approach specifically added an interaction term because of the clear distinction in

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patterns seen when the sample were grouped by dementia status. The more frequent reports of falling observed amongst those with a dementia diagnosis are consistent with clinical expectations. It may be that the neuropathological burden is so extreme in dementia as to outweigh any specific factors affecting motor control, hence few such effects can be detected. Clearly there is also the possibility that falls were poorly reported by people with dementia, though the attempts to allow for this with proxy reporting are discussed above. There is some evidence from fall risk factors research that frail older people with the highest levels of impairments – most severe dementia and immobility – fall less than those with considerable impairment who maintain some limited mobility (51) and our results may reflect this pattern. It may be that those with the highest levels of impairments have fewer opportunities to fall. More studies are required to clarify this.

There are difficulties comparing our results with MRI studies. Many MRI studies present total scores for white matter lesions (WML) without investigating what each type of hyperintensity represents. Indeed, it has been previously noted that WML as seen on MRI are heterogeneous and require careful classification (52). The various white matter lesions seen in MRI have been successfully linked with pathology seen after autopsy (11). Further studies to clarify the relationship between lesions seen in grey matter with MRI and pathology seen after autopsy are needed. Our semi-quantitative measures for microinfarcts, gliosis, perivascular space expansion or demyelination may not correlate directly to the quantitative measures used in imaging studies, making direct comparisons difficult.

Some imaging studies have investigated mobility and function relative to lesions in specific locations and have found specific periventricular or deep white effects, though the results are conflicting (24, 25, 53, 54). Our measures of presence and/or severity for each lesion are limited in this respect. It is not possible to say whether the type,

extent or location of lesions found in our study are specific to increased risk of falling or whether the lesions affect gait and balance via a more global mechanism involving executive function and the frontal-subcortical motor networks(6, 27).

Many of the pathologies associated with gait and balance disturbances are also associated with cognitive change, supporting the possibility of global rather than specific effects (53). Pathologies associated with falling are neither necessary, as shown by a subgroup of falling elderly with no clear pathology (55), nor specific, as similar burdens of lesions are shared by patients who develop gait and balance disorders and patients who do not (56). The association between falls and cognitive impairment, whether diagnosed as dementia or not, is well established (2). That neurological mechanisms may be common to both cognition and motor function also fits with clinical observation and research evidence that fall risk increases with cognitive decline and is linked to performance in dual tasks involving simultaneous demands on cognitive and mobility control pathways (57, 58). However, our findings remain unchanged when we re-analysed adjusting for MMSE score. A recent prospective community study found executive function deficits predicted increased falls risk even in healthy older adults (59). Such findings merit further investigation with imaging in population-based samples across the cognitive spectrum, questions that new research underway may be able to address (60).

While studies have found associations between tangles in the substantia nigra and mobility impairments (34, 35), our results from this region are conflicting: greater severity of tangles appeared to be associated with fewer reports of falling amongst those with dementia but not in those without dementia, nor were Lewy bodies or neuronal loss related to falling in either sub-group. This may simply be a chance finding due to sample size or an artefact of measurement error, for instance the under-estimation of pathology due to the tissue sampling protocol and the coarse measures

used. This may also reflect the pattern of fewer falls in those with the greatest impairments discussed above. Further studies are needed to replicate or refute these anomalous results.

Various studies have found significant associations between atrophy and mobility impairments(28) (21) (20). Our measure of association between atrophy and falling is small and not significant. This lack of significance may be due both to the very high proportion of the sample in which atrophy was noted and to the imprecision of the atrophy rating and again merits further investigation.

Another question for future research is whether our findings in an "older old" cohort would differ in younger old people. Hip fractures were independently associated with diffuse WML in subjects less than 80 years, but this association was not detected in subjects older than 80 (23). In contrast, our study does find an association between white matter pallor and falls in donors aged over 80. The prevalence of cognitive impairment and dementia close to death has been shown to rise steeply with older age (61) and falls are also more common in advance old age (43), but how these clinical syndromes interplay with neuropathology is still unclear, as is the relationship between neuropathology and dementia in advanced old age (62).

Classification of mobility impairments that may increase the risk of falling in the older population is currently unclear in the neuropathology literature. Gait disorders (15, 29) vascular Parkinsonism (56), extrapyramidal signs (6) and mild Parkinsonian signs (7) are terminologies used to reflect similar gait and balance disturbances. There may be continua here crossing diagnostic boundaries related to severity of clinical symptoms. The subclinical pathology associated with mobility impairment also lacks rigorous terminology. Leukoaraiosis (26), (age related) white matter changes (15) and white matter lesions (13, 14) are all terms referring to similar neuropathological lesions in

white matter. The lack of solid terminology leads to confusion in the literature and clarification is urgently needed.

Many vascular factors were associated with falls in our sub-group without dementia, though only microinfarcts were associated with falling in our sub-group with dementia. There may be multiple underlying mechanisms with the potential to contribute to mobility impairment. Type, extent and location of lesions may have quite distinct effects. Although we attempted to differentiate these features we are aware that our methods, as with many others', may not have adequately identified their independent and possibly confounding effects. Cerebrovascular disease – the common aetiology underlying the factors that our analyses have highlighted – is potentially preventable so these findings have important implications. Further studies are needed to advance understanding of the mechanisms at work, particularly research comparing in vivo imaging with subsequent post-mortem findings in relation to clinical evidence, in order that neuro-epidemiology may be translated into public health benefit.

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Ethical approval

Each phase of the CC75C study has been approved by Cambridge Research Ethics Committee.

Contributors

Key contributions to this research were made by members of the CC75C neuropathology collaboration, particularly RH, who helped establish the brain banking facility, and AO'S, who helped recruit the donors and maintained liaison with their families. TD, FEM, CB, EP, FAH and JF are current principal investigators. CB FAH and EP were principal investigators involved in setting up the Cambridge Project for Later Life and were responsible for developing the neuropathology research arm with Claude Wischik. Since then JHX has led the neuropathology for most of the study duration. CB and TD conducted the blinded clinical diagnostic review for inter-rater reliability and up-dating on the previous panel review by past collaborators. SH has been part of the neuropathology team and conducted the literature review that informed the analyses. KR is the study statistician who conducted all the analyses with guidance from FM and CB. JF advised on the falls data. SH, KR and JF wrote the

initial drafts and incorporated comments from co-authors. KR is the statistical guarantor for the paper.

Competing interests

None declared.

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Table 1. Characteristics of the neuropathology dataset by falling status at death

Characteristic	Tendency to fall status							
	No report (n=49)		One report (n=45)		2+ reports (n=118)		Total (N=212)	
	n	(%)	n	(%)	n	(%)	n	(%)
Sex								
Men	27	(55%)	12	(27%)	23	(19%)	62	(29%)
Women	22	(45%)	33	(73%)	95	(81%)	150	(71%)
Dementia status								
No dementia	27	(55%)	23	(51%)	49	(42%)	99	(47%)
Dementia	22	(45%)	22	(49%)	69	(58%)	113	(53%)
History of stroke								
No	36	(73%)	27	(60%)	57	(48%)	120	(57%)
Yes	13	(27%)	18	(40%)	61	(52%)	92	(43%)
	mean	(SD)	mean	(SD)	mean	(SD)	mean	(SD)
Age at death, years	89.8	(3.6)	90.1	(3.9)	91.8	(4.6)	91.0	(4.3)
Follow-up time, years	9.1	(3.5)	10.2	(3.1)	10.0	(4.2)	9.8	(3.8)
	median	(IQR)	median	(IQR)	median	(IQR)	median	(IQR)
Time from last survey to death, years	1.6	(0.8 - 2.3)	1.8	(1.0 - 2.5)	1.6	(0.7 - 2.7)	1.6	(0.8 - 2.6)
Time from last fall report to death, months	6.8	(0.0 - 20.3)	0.0	(0.0 - 17.6)	1.1	(0.0 - 13.3)	0.7	(0.0 - 17.9)

Table 2. Number of individuals (percentage) with specific neuropathological findings by falling and dementia status

Neuropathological variable		No dementia						Dementia						Total					
		No report (n=27)		One report (n=23)		2+ reports (n=49)		No report (n=22)		One report (n=22)		2+ reports (n=69)		No report (n=49)		One report (n=45)		2+ reports (n=	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Brain atrophy																			
Gross brain atrophy	No	6	23	5	22	5	11	0		1	5	6	9	6	13	6	13	11	
	Yes	20	77	18	78	41	89	22	100	21	96	61	91	42	88	39	87	102	
Enlarged ventricles	None	17	65	9	39	14	30	6	27	8	36	24	36	23	48	17	38	38	
	Sparse	7	27	12	52	22	48	5	23	6	27	23	34	12	25	18	40	45	
	Moderate	2	8	2	9	10	22	9	41	6	27	19	28	11	23	8	18	29	
	Severe	0		0		0		2	9	2	9	1	1	2	4	2	4	1	
Neocortical widened sulci	None	6	22	5	22	3	6	1	5	1	5	7	10	7	15	6	13	10	9
	Sparse	10	37	10	43	29	59	9	41	6	27	21	30	19	40	16	36	50	44
	Moderate	10	37	8	35	13	27	9	41	13	59	34	49	19	40	21	47	47	42
	Severe	0		0		1	2	3	14	2	9	5	7	3	6	2	4	6	
White matter pallor																			
Overall	No	21	88	13	59	21	49	8	40	8	38	27	44	29	66	21	49	48	
	Yes	3	13	9	41	22	51	12	60	13	62	35	57	15	34	22	51	57	
Cortex	No	21	88	13	59	23	54	9	45	8	38	29	47	30	68	21	49	52	
	Yes	3	13	9	41	20	47	11	55	13	62	33	53	14	32	22	51	53	
Deep White	No	24	100	22	100	38	91	16	80	18	86	54	87	40	91	40	93	92	
	Yes	0		0		4	10	4	20	3	14	8	13	4	9	3	7	12	
Cerebrovascular disease																			
Macroscopic atherosclerosis	None	13	50	10	44	16	34	12	55	6	27	24	37	25	52	16	36	40	
	Sparse	6	46	5	39	18	58	5	50	7	44	17	42	11	48	12	41	35	
	Moderate	2	6	2	7	5	10	3	13	3	11	13	16	5	9	5	9	18	
	Severe	5	16	6	21	8	14	2	8	6	21	11	14	7	13	12	21	19	

Microscopic atherosclerosis	No	26	96	20	87	37	76	18	82	18	82	57	84	44	90	38	84	94
	Yes	1	4	3	13	12	25	4	18	4	18	11	16	5	10	7	16	23
Arteriolosclerosis	No	7	26	12	52	11	23	3	14	5	23	20	29	10	20	17	38	31
	Yes	20	74	11	48	38	78	19	86	17	77	49	71	39	80	28	62	87
Perivascular gliosis	No	25	93	21	96	45	92	20	91	21	96	60	87	45	92	42	96	105
	Yes	2	7	1	5	4	8	2	9	1	5	9	13	4	8	2	5	13
V-R space expansion																		
Cortex	No	16	76	15	79	24	62	11	61	12	63	30	55	27	69	27	71	54
	Yes	5	24	4	21	15	39	7	39	7	37	25	46	12	31	11	29	40
White matter	No	12	57	9	47	9	24	4	22	7	37	26	46	16	41	16	42	35
	Yes	9	43	10	53	29	76	14	78	12	63	30	54	23	59	22	58	59
Deep grey	No	10	48	9	50	11	30	4	22	3	16	21	38	14	36	12	32	32
	Yes	11	52	9	50	26	70	14	78	16	84	35	63	25	64	25	68	61
Microinfarcts																		
Overall	No	18	75	10	46	15	39	10	56	8	42	20	33	28	67	18	44	35
	Yes	6	25	12	55	24	62	8	44	11	58	41	67	14	33	23	56	65
White matter	No	23	96	19	86	32	84	17	94	16	84	47	83	40	95	35	85	79
	Yes	1	4	3	14	6	16	1	6	3	16	10	18	2	5	6	15	16
Grey matter	No	18	75	10	46	16	44	10	56	8	42	22	39	28	67	18	44	38
	Yes	6	25	12	55	22	58	8	44	11	58	35	61	14	33	23	56	57
Substantia nigra																		
Neuronal loss	None	11	41	6	26	19	40	5	23	4	18	27	39	16	33	10	22	46
	Sparse	12	44	12	52	21	45	11	50	11	50	25	36	23	47	23	51	46
	Moderate	4	15	4	17	5	11	6	27	6	27	13	19	10	20	10	22	18
	Severe	0		1	4	2	4	0		1	5	4	6	0		2	4	6
Any Lewy bodies	No	25	93	21	91	43	96	19	86	17	81	61	88	44	90	38	86	104
	Yes	2	7	2	9	2	4	3	14	4	19	8	12	5	10	6	14	10
Tangles	None	18	67	17	74	19	41	5	23	7	32	25	38	23	47	24	53	44
	Sparse	4	15	3	13	18	39	6	27	6	27	23	35	10	20	9	20	41

Moderate	2	7	1	4	5	11	8	36	2	9	7	11	10	20	3	7	12
Severe	3	11	2	9	4	9	3	14	7	32	11	17	6	12	9	20	15

* Individuals with missing scores are not included for calculation of percentages.

Table 3. Ordinal logistic regression predicting fall status: unadjusted, adjusted and multivariable results

Neuropathological variable	Unadjusted risks			Dementia status	Adjusted* risks			Mulitvariable adjusted** risks		
	ORğ	95% CI	p		ORğ	95% CI	p	ORğ	95% CI	p
Brain atrophy										
Gross brain atrophy	1.3	0.6 - 2.9	0.52	No dementia	2.3	0.8 - 6.3	0.11			
				Dementia	0.2	0.0 - 1.8	0.15			
Moderate/severe enlarged ventricles	1.0	0.6 – 1.9	0.90	No dementia	2.7	0.8 - 9.5	0.12			
				Dementia	0.5	0.2 – 1.1	0.08			
Moderate/severe neocortical widened sulci	1.0	0.6 – 1.7	0.96	No dementia	0.8	0.3 - 1.8	0.55			
				Dementia	0.9	0.4 – 1.9	0.76			
White matter pallor										
Overall	1.8	1.0 - 3.0	0.04	No dementia	2.7	1.1 - 6.6	0.02	2.8	1.0 - 7.3	0.04
				Dementia	0.9	0.4 - 2.0	0.81	0.6	0.2 - 1.4	0.24
Cortex	1.6	0.9 - 2.8	0.08	No dementia	2.4	1.0 - 5.7	0.05			
				Dementia	0.9	0.4 - 2.0	0.77			
Cerebrovascular disease										
Macroscopic atherosclerosis	1.6	0.9 - 2.7	0.10	No dementia	1.8	0.8 - 4.0	0.15			
				Dementia	1.3	0.6 - 2.8	0.56			
Microscopic atherosclerosis	1.7	0.8 - 3.6	0.14	No dementia	4.5	1.4 - 15.0	0.02	3.8	1.0 - 14.1	0.04
				Dementia	0.8	0.3 - 2.1	0.62	0.9	0.3 - 2.9	0.92
V-R space expansion										
Cortex	1.6	0.9 - 3.1	0.11	No dementia	2.1	0.8 - 5.6	0.15			
				Dementia	1.4	0.6 - 3.2	0.47			
White matter	1.2	0.6 - 2.1	0.60	No dementia	2.5	1.0 - 6.2	0.04			
				Dementia	0.4	0.2 - 1.0	0.05			

Deep grey	1.0	0.6 - 1.9	0.95	No dementia	1.8	0.7 - 4.5	0.19			
				Dementia	0.5	0.2 - 1.3	0.13			
Microinfarcts										
Overall	2.6	1.5 - 4.6	0.00	No dementia	2.8	1.2 - 6.4	0.02	1.6	0.6 - 4.0	0.35
				Dementia	2.3	1.0 - 5.4	0.05	2.7	1.1 - 6.5	0.02
Grey matter	2.1	1.2 - 3.8	0.01	No dementia	2.5	1.1 - 5.8	0.03			
				Dementia	1.7	0.7 - 4.0	0.20			
Substantia nigra										
Moderate/severe neuronal loss	0.9	0.5 - 1.7	0.81	No dementia	1.1	0.4 - 3.2	0.79			
				Dementia	0.8	0.3 - 1.8	0.56			
Lewy bodies	0.8	0.3 - 1.8	0.60	No dementia	0.9	0.2 - 3.9	0.85			
				Dementia	1.0	0.3 - 2.9	1.00			
Moderate/severe tangles	0.7	0.4 - 1.3	0.28	No dementia	1.1	0.4 - 3.1	0.90			
				Dementia	0.3	0.1 - 0.7	0.003			

* Adjusted for age, dementia status, stroke and results stratified by dementia status

** Adjusted for age, dementia status, stroke and all other variables in the model

§ Ordinal OR, i.e. the OR of the '2+ falls group' compared to the combined 'no report' and 'one report' groups and the OR of the combined 'one report' and '2+ reports' groups to the 'no report' group

Figure 1. Proportions of donors with (a) gross atrophy, (b) microscopic atherosclerosis, (c) white matter pallor, (d) cortical V-R space expansion, (e) microinfarcts, and (f) neuronal loss in the substantia nigra by falling status in those with dementia (solid line) compared to those without dementia (dashed line).
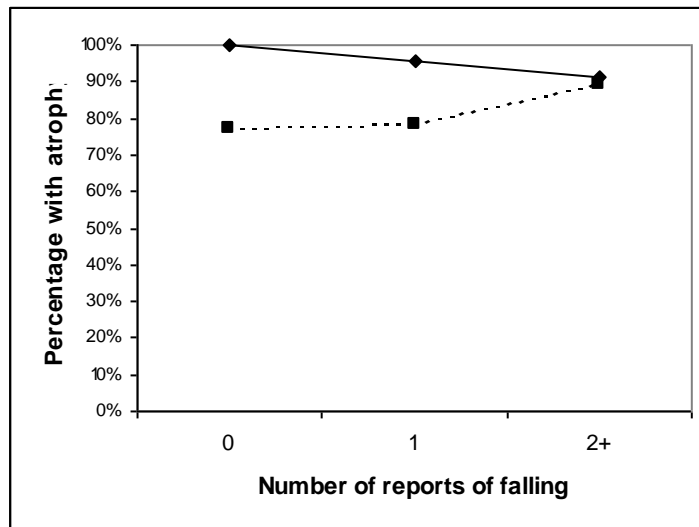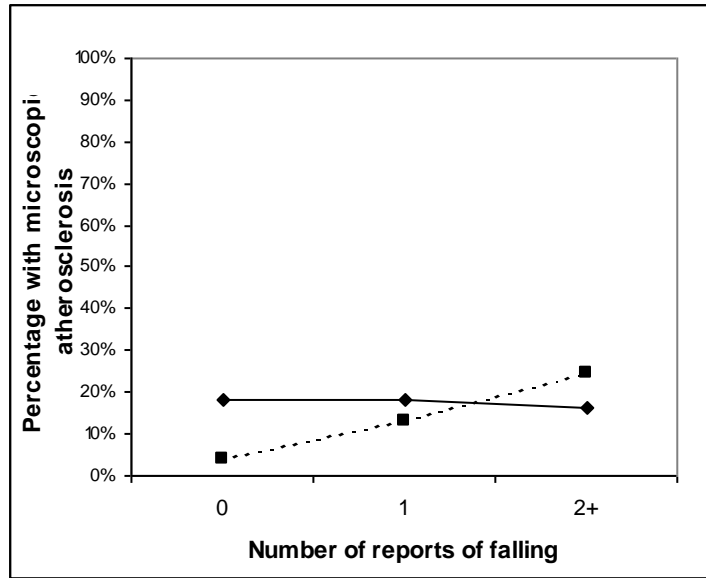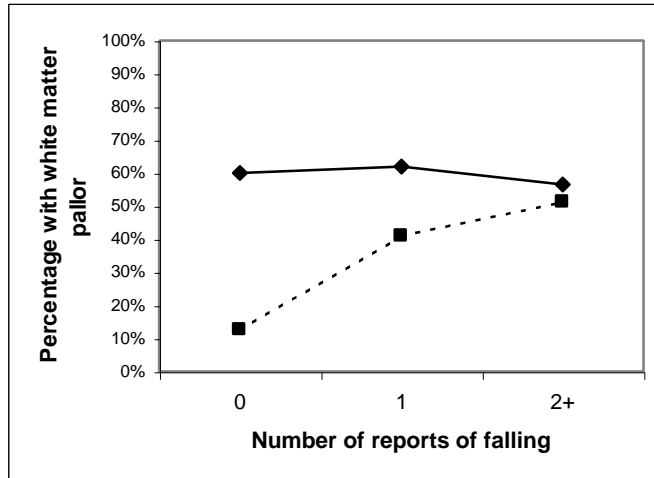
Fig 1(a).

Fig 1(b).

Percentage with microscopic atherosclerosis vs Number of reports of falling. The y-axis ranges from 0% to 100% and the x-axis shows values 0, 1, and 2+.
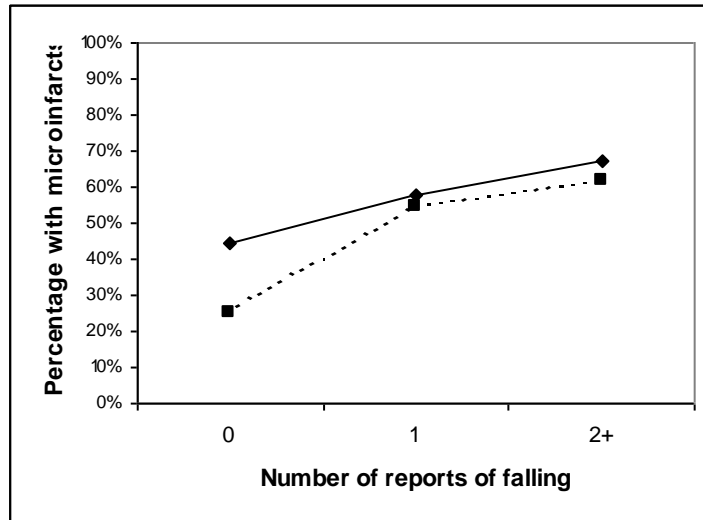
Fig 1(c).

Fig 1(d).

Fig 1(e).

Fig 1(f).