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Age modifies the association between apathy and recurrent falling in Dutch ambulant older persons with a high fall risk
Recurrent falling in Dutch outpatients, does apathy play a role?

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ABSTRACT

Apathy, a common and disabling behavioural syndrome in older persons, has been associated with impaired physical performance and executive dysfunction. Both are fall risk factors and they share pathophysiological pathway. We cross-sectionally examined the association between apathy and recurrent falling (≥2 falls in the past 12 months) and number of falls in the past 12 months in 243 outpatients aged ≥65 years with ≥3 fall risk-factors visiting a fall-clinic after a fall. We calculated Odds Ratio's (ORs), Incidence Rate Ratio's (IRRs) and their 95% Confidential Intervals (CI95) using multivariable regression and negative binomial regression analyses. We adjusted for cognitive functioning, depression, the use of fall risk increasing drugs, visual impairment, urine incontinence, comorbidity, smoking, use of alcohol, body mass index (BMI), and the number of months between assessment of fall risk and of apathy. We assessed effect modification by age and gender.

In our study, apathy was independently associated with recurrent falling in patients aged 65–75 years: OR 2.8 (CI95 1.0–7.7). Overall, patients with apathy experienced 1.46 times as many falls in the past 12 months compared to patients without apathy (IRR 1.46 (CI95 1.0–2.1).

To conclude, in high fall-risk older outpatients, apathy was cross-sectionally associated with recurrent falling in patients aged 65–75 years and the number of falls. Apathy appeared to be especially relevant in relation to falling in this age group. Whether apathy predicts recurrent falling is yet to be determined.

1. Introduction

Accidental falls are a major health care concern in older individuals. Approximately one third of community-living persons aged 65 or above experience a fall each year (Gillespie et al., 2012), with approximately 50% falling at least two times annually (Tromp et al., 1998). Both fall rate and fall-related injury rates have been growing at a worrying rate in the last few decades. Fall-related hospital admissions in the Netherlands have increased by 63% from 2006 through 2015 (Draisma, 2016), resulting in straining hospital capacity and increasing health care expenditure. For older persons, falling often results in a cascade of negative outcomes, such as functional decline, institutionalization or even mortality (Tinetti & Speechley, 1989; Tinetti et al., 1988). Among fallers, recurrent fallers have been suggested to form a distinct group as compared to single fallers, with recurrent falling mostly defined as experiencing at least two falls per given time unit (Luukinen et al., 1995; Askari et al., 2013; Raffard et al., 2016). Since one fall may occur by chance, the repetition of the event suggests an increased vulnerability for falling. Several risk factors for (recurrent) falling have been identified over the years, including cognitive disorders (Askari et al.,

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2013), experiencing functional difficulties and impaired balance (Burton et al., 2018). In order to make fall preventive strategies as effective as possible, it is important to scrutinize new possible fall risk factors and its accompanying pathways leading to fall incidents. Apathy, which has been associated with several negative outcomes in various older populations, may be such a new and unexplored fall risk factor.

Apathy has widely been recognized as a disabling neuropsychiatric syndrome after its first description by Marin et al. in 1991 (Marin, 1991). Although there is no clear consensus, apathy is usually defined as a motivational disorder, affecting motor (initiative), cognitive (interest) and emotional aspects of behavior (Raffard et al., 2016; Marin, 1991; Onyike et al., 2007). Apathy precedes cognitive decline in persons with neurocognitive disorders (Lanctot et al., 2017; Pagonabarraga et al., 2015), but also in community-dwelling older persons without dementia (Clarke et al., 2010; van Dalen et al., 2018). In divergent study samples, apathy has mainly been associated with executive dysfunctioning (Lohner et al., 2017; Kawagoe et al., 2017; Douven et al., 2018). However, in persons with mild cognitive impairment (MCI), apathy also has been associated with worse performance on overall cognitive functioning, attention and imprinting (Vloeberghs et al., 2018). Despite the fact that there is increasing evidence that apathy and depression should be considered as separate entities, apathy is frequently misdiagnosed as depression due to an overlap of symptoms such as psychomotor retardation, anhedonia and diminished enthusiasm about usual interests (Onyike et al., 2007; Pagonabarraga et al., 2015). Apathy and depression are thought to have a (partly) different pathophysiology and thus perhaps require different treatment strategies (Yuen et al., 2015; Yuen et al., 2014; Groeneweg-Koolhoven et al., 2016; Mortby et al., 2012). With regard to physical functioning and joint occurrence of apathy and depression in older persons, it was suggested that supplementary treatment of apathy may have a positive impact on disability (Yuen et al., 2015). Furthermore, recently it was demonstrated that apathy predicted decline in physical functioning in older persons without dementia, independent of depression severity (Henstra et al., 2018).

Besides in depressed patients, the negative impact of apathy on physical functioning has also been demonstrated in persons with Parkinson's Disease (Pedersen et al., 2009) and cognitive impairment or dementia (van Reekum et al., 2005; Starkstein et al., 2001; van der Linde et al., 2016), but also in older persons without dementia or other psychiatric diseases (Ayers et al., 2017a).Next, an association between apathy, frontal white matter lesions and executive dysfunction has been determined in several previous studies (Hollocks et al., 2015), due to a disruption of fronto-striatal circuits (Taylor et al., 2013; Brodaty et al., 2005; Wen et al., 2016; Sigmundsson et al., 2001; Sener et al., 2015). Separately, both frontal white matter lesions and executive dysfunction have been associated with gait and balance impairment (Rapport et al., 1998; Zheng et al., 2011), as well as an increased risk of falling (Zheng et al., 2011; Muir et al., 2012; Blahak et al., 2009). Therefore, an association between apathy and falling appears likely. However, to our knowledge, this association has not yet been addressed in the literature before. If we are able to identify apathy as a risk-factor for falling, this may be a first step towards an identification of a new, potentially modifiable fall-risk factor.

This study aims to determine a potential association between apathy and recurrent falling. We hypothesize that apathy is associated with recurrent falling in a Dutch cohort of older individuals visiting a fall clinic, irrespective of cognitive functioning and depressive symptoms.

2. Methods

2.1. Study population and source of the data

For this cross-sectional study, from 01-01-2006 to 31-12-2015 data were extracted from an ongoing observational prospective cohort study involving Dutch patients aged 65 years and older visiting the outpatient fall-clinic at the Academic Medical Centre (AMC) in Amsterdam (Scheffer et al., 2013). The medical ethics committee of the Academic Medical Center (Amsterdam) approved this study and waived the necessity for informed consent because of the observational design. All patients gave informed consent for use of the data for research purposes.

Data were gathered using the Combined Amsterdam and Rotterdam Evaluation of Falls (CAREFALL) Triage Instrument (CTI). This is a validated self-reported questionnaire which assesses modifiable risk-factors for recurrent falls in elderly Accident & Emergency room (A&E) patients (Scheffer et al., 2013; Boele van Hensbroek et al., 2009). Data on the number of falls in the past 12 months are collected via the CTI. All patients aged 65 years and older presenting with a fall at the A&E at the AMC received a CTI questionnaire within one week after the visit. After 2 weeks, non-responders received a reminder call. Patients with an increased risk of falling, defined by the presence of 3 or more risk factors identified by the CTI, were contacted and invited to attend the fall prevention clinic (FPC). Patients with 1–2 fall risk-factors were invited to the CAREFALL-A clinic, which covers a more basic outpatient service than the fall prevention clinic. Additional information on patient characteristics and possible contributing factors to falling was gathered and specified during the visit to the fall clinic. Patients who visited the fall-clinic > 6 months after filling in the CTI-questionnaire were excluded from the study, as were patients with missing data on symptoms of depression and apathy (patients without information on 15-item Geriatric Depression Scale (GDS-15) and patients with > 1 item missing on the GDS-apathy-3 (GDS3-A), a subscale of the GDS-15).

2.2. Apathy

For the assessment of apathy, the GDS3-A was used, comprising three questions of the GDS-15 (answer yes/no) ((1) Have you dropped many of your activities and interests?; (2) Do you prefer to stay at home, rather than going out and doing new things?; and (3) Do you feel full of energy?). The GDS3-A indicates that apathy is present with ≥2 positive answers and apathy is absent with ≤1 positive answer. The scale has been validated in previous studies in community dwelling older persons (van der Mast et al., 2008; Ligthart et al., 2012).

2.3. Primary and secondary outcome measures

Recurrent falling registered through use of the CTI was the primary outcome, defined as ≥2 fall incidents the past 12 months. This is in alignment with previous literature where recurrent falling is frequently defined as ≥2 falls per 6–12 months (Luukinen et al., 1995; Askari et al., 2013; Masud & Morris, 2001). ≥3 falls in 12 months has been mentioned in previous studies as alternative definition of recurrent falling (Rapport et al., 1998). Therefore, as secondary outcomes ≥3 fall incidents and number of falls during the past 12 months were assessed.

2.4. Co-variables

Various variables were examined as co-variables: age, gender, cognitive functioning, depression, the use of Fall Risk Increasing Drugs, visual impairment, urine incontinence, comorbidity, smoking, use of alcohol, body mass index (BMI), balance, physical activity and the number of months between completing the CTI and GDS. Cognitive functioning was assessed with the Mini Mental State Examination. Depression was assessed with the Geriatric Depression Scale-12 (GDS-12D), a subscale of the GDS-15, excluding the three items of apathy (van der Mast et al., 2008). A predefined list of known Fall Risk Increasing Drugs (FRIDs) as described in previous studies was used (van der Velde et al., 2007). Urine incontinence and visual impairment were based on self-report (yes/no). Comorbidity was measured with the Charlson Comorbidity Index, a validated method of classifying

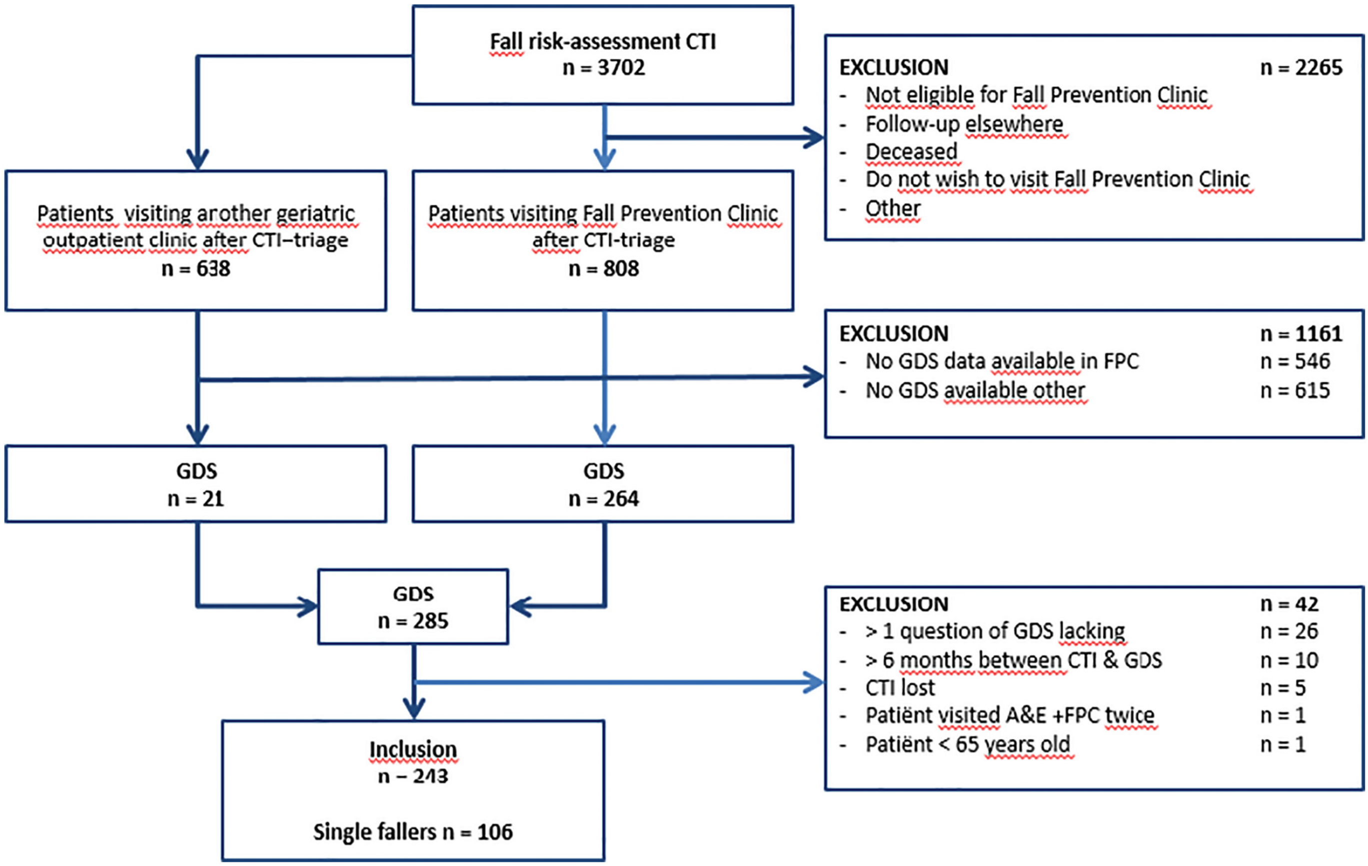

Fig. 1. Flowchart revealing the included study-population.

prognostic comorbidity (Charlson et al., 1994). Alcohol use was categorised into no/limited alcohol intake, moderate alcohol intake and excessive alcohol intake. Balance was assessed with the Berg Balance Scale, a 14-items scale with higher scores indicating better balance (Berg et al., 1992). Physical activity was assessed through a CTI question: "How often do you exercise?" Possible answers were: daily (30 min of walking, cycling or swimming), 3 times a week, weekly, monthly or (almost) never (Scheffer et al., 2013).

2.5. Statistical analyses

All analyses were performed using the Statistical Package for the Social Sciences IBM SPSS Statistics 23 (IBM, Armonk, New York, United States). The distribution of baseline characteristics and primary outcome measures was examined in order to analyze differences between patients with and without apathy (age, months between CTI and GDS, BMI, cognition, depression, number of medicines, number of cardiovascular medicines, number of psychotropic medicines, number of Fall Risk Inducing Drugs, Berg Balance Scale, Fear of Falling, number of falls in past 12 months). For comparison of continuous variables, we used a *t*-test for normally distributed data and a Mann-Whitney *U* Test for non-normally distributed data. The difference in categorical and dichotomous variables was tested using a Chi square test. Binary logistic regression analyses were used to calculate Odds Ratios (OR) with 95% Confidence Intervals (95% CI) for the association between apathy and recurrent falling. First, ORs were calculated in a crude model containing sex and age (Model A). Second, we investigated the following variables as potential confounders: gender, age (except for the age-stratified analyses), months between CTI and apathy assessment, smoking, use of alcohol, MMSE-scores, depression, Charlson comorbidity index, number of Fall Risk Inducing Drugs, urine incontinence and visual impairment. The potential confounders were separately added to the crude model. Parameters that changed the regression coefficient by > 10% were added to the model, resulting in a multivariable logistic regression analysis (Model B). Impaired balance and lower physical activity were examined as intermediates and were separately added to the fully adjusted model. We used multiple imputations for the MMSE-score since 26/243 (11%) had missing data. For imputation, we used 7 baseline variables with well-nigh complete data (age, gender, GDS-scores, presence of apathy, depression (GDS 12), Charlson comorbidity index, smoking and visual impairment, 3 missing values maximum). Since 11% of MMSE-score was missing, 11 datasets were used. MMSE-scores were only a confounder in the logistic regression analyses but not in the negative binomial regression analyses. As the negative binomial regression analyses could not be performed on the pooled dataset, only the logistic regression analyses were performed on the pooled data-set. In order to assessed whether absence of MMSE-scores ($N = 26$) influenced the outcomes, we performed sensitivity-analyses in a dataset excluding all patients with missing data on MMSE ($N = 217$) (Results available as appendices) Next, effect modification by gender and age was examined. A product term was created (effect modifier ∗ apathy) which was added to the crude model. Effect modification was present if p for effect modification < 0.1, after which the analyses were stratified for the effect modifier. Finally, considered mediation was present if the parameter gave a decrease of the regression coefficient of > 10% in the fully adjusted models. To examine the association between apathy and the number of falls, an Incidence Rate Ratio (IRR) with its 95% CI was calculated using a negative binominal regression analysis since this regression analysis handles overdispersion better than the Poisson regression (Byers et al., 2003). One outlier was removed. To identify confounders, a similar procedure as described above was used. Furthermore, to distinguish between the impact of both apathy and depression on falls, we performed logistic regression analyses with depression (defined as GDS-

15 > 5 points) as determinant instead of apathy to compare. We also calculated Receiver Operating Curves (ROC) for the comparison of both apathy and depression in relation to recurrent falling (≥3) by using STATA ROCCOMP. Finally, we calculated a Pearson correlation coefficient to determine the correlation between apathy and depression. Since the GDS-3A is a sub-score of the GDS-15, we expected high correlation between apathy and depression assessed with GDS-15. We therefore used two definitions of depression (GDS-15 and GDS-12) to determine the correlation between apathy and depression.

3. Results

From 01-02-2006 to 31-12-2015, in total 808 patients visited the outpatient fall-clinic following a visit to the A&E department due to a fall, of which 264 patients (32%) completed a GDS-15. Next, data on 21 additional patients with a previous fall who completed the CTI and GDS were gathered via other geriatric outpatient clinics, resulting in a total study population of 285 patients. After exclusion of 42 patients for several reasons (see Fig. 1.), a study sample of 243 patients remained. Further details on inclusion are presented in Fig. 1.

3.1. Descriptive characteristics

Demographic and clinical characteristics of the study sample are shown in Table 1.

The cohort consisted of 243 patients with an average age of 75.8 years (SD ± 7.0) and 66.3% females. Forty-six percent of the study sample satisfied the definition of apathy. Fifty-six percent of the patients was classified as recurrent faller according to the definition of ≥2 falls in the past 12 months.

There was no significant difference in prevalence of recurrent falling, defined as ≥2 falls in the past 12 months, in patients with or without apathy. Using a cutoff of ≥3 falls in the past 12 months showed a significant higher prevalence of recurrent falling in patients with apathy in comparison with patients without apathy ($p = 0.007$). Furthermore, the total number of falls in the past 12 months was higher in patients with apathy than in patients without apathy ($p = 0.014$).

3.2. The association between apathy and recurrent falling

The association between apathy and recurrent falling defined as ≥2 falls in patients aged 65 years and older was non-significant: OR Model A 1.4 (95% CI 0.8–2.3).

However, after stratification for age, apathy was associated with recurrent falling in patients aged 65–75 years, but not in patients aged ≥75 years (OR Model A 2.5 (95% CI 1.2–5.5), OR adjusted model 2.8 (95% CI 1.0–7.7) Table 2). Using a cutoff of ≥3 falls in the past 12 months in the overall sample, apathy increased the odds of recurrent falling with an OR of 2.3 (95% CI 1.3–4.2) in model A and 2.1 (95% CI 1.1–4.1) after adjustment for confounders (model B). The association between apathy and recurrent falling with a cutoff ≥3 falls per 12 months was also modified by age. The direction of the effect modification was similar to the first analysis (Table 2). For both definitions of recurrent falling, gender did not act as an effect modifier.

3.3. Mediation

For both definitions of recurrent falling, Berg Balance Scale and physical activity were intermediates in the association between apathy and recurrent falling (Table 3).

3.4. The association between apathy and number of falls

In Model A, the adjusted Incidence Rate Ratio (IRR) of apathy for number of falls was 1.69 (95% CI 1.24–2.31). After adjustment for confounders, the IRR was 1.46 (95% CI 1.0–2.1) meaning that patients with apathy experienced 1.46 times as many falls in the past 12 months compared to patients without apathy. Balance and physical activity were no mediators.

Table 1
Descriptive characteristics for total study sample and individuals with and without apathy.

Characteristics	Total	Apathy	No apathy	*p*-Value
	N = 243	*N* = 113	*N* = 130	
Women (%)	161 (66.3)	72 (63.7)	89 (68.5)	0.435
Age (years)	75.8 ± 7.0	75.8 ± 6.9	75.7 ± 7.1	0.913[a]
Months between CTI and GDS	2 (1–3)	2 (0.5–3)	2 (1–3)	0.377
BMI (kg/m2)	26.5 ± 4.8	26.7 ± 4.9	26.3 ± 4.6	0.646[a]
Smoking: yes (%)	36 (15.1)	21 (18.9)	15 (11.7)	0.121
Use of alcohol (%)				0.111
No/limited alcohol intake	120 (51.8)	64 (58.2)	56 (44.8)	
Moderate alcohol intake	90 (38.3)	37 (33.6)	53 (42.2)	
Excessive alcohol intake	25 (10.6)	9 (8.2)	16 (12.8)	
Living situation (%)				
Home dwelling	229 (97)	109 (98.2)	120 (96.0)	0.542
Nursing home	7 (3)	2 (1.8)	5 (4)	
Functionality				
Receiving help in ADL (%)	104 (44.1)	66 (59.5)	64 (58.2)	< 0.001
Use of mobility aid before last fall (%)	96 (39.7)	63 (55.8)	37 (33.6)	< 0.001
KATZ-15 (%)	2 (0–5)	4 (2–7)	9 (8.2)	< 0.001
Physical activity (%)				0.016
Daily	95 (40.6)	38 (45.1)	57 (49.9)	
3 times a week	44 (18.8)	20 (20.9)	24 (23.1)	
Weekly	19 (8.1)	6 (9.0)	13 (10.6)	
Monthly	3 (1.3)	3 (2.7)	0 (0)	
(almost) Never	73 (31.2)	44 (39.6)	29 (23.6)	
Cognition				
MMSE (points)	28 (25–29)	28 (24–29)	28 (25–29)	0.041
Depression				
GDS-12, points (0 – 12)	1.5 (0.25–4)	3 (1–6)	1 (0–3)	< 0.001
Comorbidity				
Charlson comorbidity index	1 (0–2)	1 (1–3)	1 (0–2)	0.009
Cardiovascular diseases (%)	183 (75.3)	85 (75.2)	98 (75.4)	0.976
Number of medicines	6.1 ± 3.6	7.4 ± 3.7	5.0 ± 3.0	< 0.001[a]
Number of cardiovascular medicines	1.6 ± 1.5	1.7 ± 1.6	1.5 ± 1.4	0.237[a]
Number of psychotropic medicines	0.4 ± 0.7	0.5 ± 0.8	0.3 ± 0.7	0.034[a]
Number of FRID	3.7 ± 2.4	4.3 ± 2.5	3.2 ± 2.1	< 0.001[a]
Urine Incontinence (%)	68 (28.9)	36 (33.6)	32 (25)	0.146
Visual impairment (%)	100 (41.7)	59 (52.2)	41 (32.3)	0.002
Berg Balance Scale, points (0–56)	50 (41–54)	45 (34–51)	52 (48–52)	< 0.001
Fear of Falling (FES), points (0 – 33)	3 (1–6)	5 (2–9.75)	2 (0–5)	< 0.001
Falling				
Recurrent falling (≥2) (%)	137 (56.4)	69 (61.1)	69 (53.1)	0.266
Recurrent falling (≥3) (%)	69 (31.1)	42 (40.2)	28 (23.7)	0.007
Number of falls in past 12 months	2 (1–3)	2 (1–4)	1 (1–2)	0.014

Values are numbers mean (± standard deviation, SD) or median (interquartile range, IQR).
CTI: Carefall Triage Instrument, GDS: Geriatric Depression Scale, BMI: Body Mass Index, ADL: activities of daily living.
[a] Non-parametric Mann-Whitney.

3.5. Comparison of apathy and depression in relation to falls

The Odds Ratios for the association between depression and recurrent falling defined as ≥3 falls were lower compared to the Odds Ratios for apathy and recurrent falling. Next, we compared the ROCs for apathy and depression (GDS-15) and recurrent falling (≥3) respectively. The *p*-value was 0.7308, indicating that the sensitivity and specificity of GDS-3A, and GDS-15 in relation to recurrent falling do not differ statistically. Results are depicted in Table 4.

Next, in Model A, the Incidence Rate Ratio (IRR) of depression for

Table 2
Results for logistic regression analysis of the presence of apathy and recurrent falling (≥2 and ≥3 falls in the past 12 months) stratified for age.

		Age 65–75				Age 75+			
		N	OR	95% CI	*p*-Value	N	OR	95% CI	*p*-Value
Recurrent falling (≥2)	Model A	120	2.5	(1.2–5.5)	0.018*	123	0.8	(0.4–1.7)	0.629
	Model B[a]	112	2.8	(1.0–7.7)	0.040*	107	0.5	(0.2–1.1)	0.107
Recurrent falling (≥3)	Model A	113	4.3	(1.8–10.5)	0.001*	109	1.3	(0.6–2.9)	0.536
	Model B[b]	111	5.1	(1.8–14.3)	0.002*	105	0.8	(0.3–2.2)	0.725

Model A adjusted for gender. Model B[a] adjusted model for gender, smoking, alcohol use, score on MMSE, score on GDS-12, Charlson comorbidity index, incontinence, and visual impairment Model B[b] (RF ≥ 3) adjusted model for gender, score on MMSE, score on GDS-12, Charlson comorbidity index, and visual impairment *Significance level $p < 0.05$.

Table 3
Results for logistic regression analysis on apathy and recurrent falling (≥2 and ≥3 falls in the past 12 months) including intermediates Berg Balance Scale and physical activity.

	Recurrent falling ≥ 2 falls				Recurrent falling ≥ 3 falls			
	N	OR	95%-CI	*p*-Value	N	OR	95%-CI	*p*-Value
Model A	243	1.4	(0.8–2.3)	0.211	222	2.3	(1.3–4.2)	0.005*
Model B	219	1.1	(0.6–2.0)	0.798[a]	216	2.1	(1.1–4.1)	0.025[b]*
Model C								
[a]Berg Balance Scale	185	0.9	(0.5–1.9)	0.834	182	1.7	(0.8–3.7)	0.192
[b]Physical activity	209	1.0	(0.5–1.9)	0.966	209	1.9	(1.0–3.8)	0.058

Model A adjusted for age and gender Model B[a] adjusted model for age, gender, smoking, alcohol use, score on MMSE, score on GDS-12, Charlson comorbidity index, incontinence, visual impairment.
Model B[b] adjusted model for age, gender, score on MMSE, score on GDS-12, Charlson comorbidity index and visual impairment.
Model C[a+b]: Model B + intermediate Berg Balance Scale or physical activity * Significance level $p < 0.05$.

Table 4
Comparison of ORs and ROCs for apathy and depression in relation to recurrent falling (≥3).

	Apathy			Depression		
	OR	95%CI	*p*-Value	OR	95%CI	*p*-Value
Model A	2.3	1.3–4.2	0.005	1.1	1.0–1.2	0.007
Model B[a+b]	2.1	1.1–4.1	0.025	1.1	1.0–1.2	0.192
ROC area	0.60	0.47–0.61		0.59	0.52–0.65	

Model A adjusted for age and gender.
Model B[a] adjusted model for age, gender, score on MMSE, score on GDS-12, Charlson comorbidity index and visual impairment.
Model B[b] adjusted model for age, gender, score on MMSE, Charlson comorbidity index and visual impairment.

the number of falls was 1.57 (95% CI 1.12–2.19). After adjustment for confounders, the IRR was 1.42 (95% CI 1.00–2.00). The correlations between apathy and depression (GDS-15 and GDS-12) were 0.64 and 0.40 respectively.

4. Discussion

In a Dutch cohort of older outpatients visiting a fall clinic apathy was independently associated with recurrent falling during the past 12 months in patients aged 65–75 years, but not in patients aged over 75 years. This association was partly explained by a poorer balance and lower physical activity. Outpatients with apathy experienced 1.46 times as many falls in the past 12 months compared to outpatients without apathy.

To our knowledge, no earlier studies have assessed an association between apathy and recurrent falls. Nevertheless, there are previous studies discussing the pathophysiological pathways leading to apathy which substantiate an association between apathy and recurrent falls. These studies show a disruption of fronto-striatal circuits to be a cause for apathy (Sigmundsson et al., 2001; Lavretsky et al., 2007), as well as executive dysfunctioning (Sener et al., 2015). The prefrontal cortex and striatum are supposedly the main regions involved in the control of apathy and executive functioning. In both regions the dopaminergic system plays an important role as a modulator (Marin, 1991; Hollocks et al., 2015). This also explains the symptomatology in Parkinson's disease, which is a neurodegenerative disease with disruption of the dopaminergic system as a core feature, in which apathy is a common symptom (Pagonabarraga et al., 2015). Since executive functioning is known to contribute to motor planning and therefore to maintain gait stability, a disruption of fronto-striatal circuits potentially is responsible of gait instability, impaired balance, and slow walking speed, which are all considered risk factors for falling.

However, since we performed a cross sectional study, we cannot make a statement about the direction of the associations between apathy and recurrent falling. Therefore, the results of this exploratory study should be interpreted with caution. Since we cross-sectionally determined the association between apathy and recurrent falling in the *past* 12 months, it is difficult to translate our results into a future fall risk. However, recently, in community-dwelling persons, apathy (also measured with GDS-3A) was shown to be longitudinally associated with frailty and decline of physical functioning (Ayers et al., 2017b). The latter are both fall risk factors. Due to the aforementioned pathophysiological pathways, and its association with frailty and decline of physical functioning, it is very well a possibility that apathy increases (recurrent) fall risk, but further studies are necessary to confirm this. Alternatively, recurrent falls may increase the risk of occurrence of apathy. In a previous study, falling appeared to be an early sign of cognitive (executive) deterioration in participants without cognitive complaints (Herman et al., 2010). If in apparently normal cognitive functioning falling is an early sign of executive dysfunctioning, hypothetically apathy (also as a dysexecutive symptom (Gansler et al., 2017)) may be predicted by falling.

Interestingly, an association between apathy and both definitions of recurrent falling was only demonstrated in patients aged 65–75 years. This may suggest that in this age group the presence of apathy potentially leads to a less active life style, resulting in impaired physical performance and therewith (recurrent) falls. This needs to be confirmed in future (prospective) studies. Our results also implicate that apathy as a fall risk factors may be (partly) age specific, which is, concerning several other fall risk factors, in line with recent literature. It was recently demonstrated that fall characteristics vary per age category (James et al., 2018). For example, middle aged fallers are more often males, in contrast to fallers aged over 65 years. In our study, the impact of apathy on recurrent falling also varied with age. Perhaps in patients aged ≥75 years, the role of apathy with regard to falling becomes less important because it is by overruled other age related fall risk factors, explaining the absence of an relationship between apathy and falling in the older old. Following this reasoning, the role of apathy with regard to falling may also be overruled by other age related fall risk factors, such as more cognitive dysfunctioning involving other cognitive domains than solely executive functioning and co-morbidity and mobility disorders. As expected, the association between apathy and recurrent falling was mediated by impaired balance, meaning that the association may be (partly) explained by impaired balance. Gait disorders (including impaired balance) are major fall risk factors and their prevalence increase with increasing age (Salzman, 2010). It was therefore unexpected that the association was only present in patients aged 65–75. However, it is known that gait disorders in older persons are multifactorial and besides prevalence-rates, also the etiology of gait disorders varies with age (Salzman, 2010). For example, in community-dwelling persons older than 88, joint pain was the main contributor to impaired mobility (Bloem et al., 1992). Perhaps, in recurrent fallers aged 65–75 years, the impact of apathy on balance and mobility is mainly caused by (isolated) impaired executive functioning, and less by other causes for impaired balance and mobility and as a result, a higher risk of recurrent falling. Thus, with increasing age, the impact of mobility disorders on (recurrent) falling increases, but with regard to the etiology of the mobility disorders, the impact of apathy on mobility disorders might be overruled by other age related diseases. Finally, also physical activity acted as an intermediate in the association between apathy and recurrent falling in persons aged 65–75. This effect was also unexpected and we can only speculate on this finding. In our study, physical activity was defined by outdoor activities. However, with increasing age, location of fall incidents moves from outdoor to indoor (James et al., 2018). Perhaps in recurrent fallers, apathy mainly diminishes physical activity in outdoor activities, which eventually results in a higher recurrent fall risk in fallers aged 65–75.

When determining the association between apathy and falling, it is important to take depressive symptoms into account. As stated in the introduction, although apathy and depression are partly overlapping syndromes, they are not interchangeable, as underlined by different ORs for apathy and depression in relation to recurrent falling. The correlation between apathy and depression assessed with the GDS-12 was 0.40, which suggests that although they are partly overlapping syndromes, apathy and depression should be assessed separately when evaluating fall risk.

The prevalence of apathy was remarkably high in our study: 46,5%. In literature, prevalence-rates of apathy have shown to be strongly depended on the population under study. In community-dwelling older persons classified as cognitively normal, with a mild cognitive syndrome and with dementia, prevalence rates of 1.4%, 3.1% and 17.3% respectively, were reported (Onyike et al., 2007). We have several possible explanations for our high prevalence of apathy. First of all, our study population represents a frail subpopulation compared to the general population of older individuals, mainly due to the inclusion criteria: patients visiting an outpatient fall clinic because of a previous fall. Secondly, retrospectively the GDS appeared to mostly have been registered on indication, in all probability favorably excluding patients without apathy. This has probably given an overestimation of the prevalence of apathy and is a limitation of our study. With regard to selection bias, this may have further occurred at various moments during the inclusion process for several reasons. Firstly, of the persons who received a CTI, < 40% (drop out 2265/3702) returned it, which is comparable to other falls and fracture liaison services (van den Berg et al., 2015). Next, of the 808 patients visiting the Fall Prevention Clinic, ± 30% was included in our final analyses. The non-participants were more often female (69 vs 64%, $p < 0.001$), and older (79 vs 75 years, $p < 0.001$). However the total number of falls in the past 12 months and living situation did not differ significantly. Another limitation was the high percentage of missing data on MMSE-scores, since cognitive performance and apathy are strongly related. However, to overcome this issue we used multiple imputations and we performed sensitivity analyses excluding all patients with missing data on MMSE-scores. The sensitivity analyses revealed, albeit reduced statistical power, similar results (Appendices A, B and C). Further limitations of the study are its cross-sectional design with retrospective gathering of data on recurrent falling, and the use of a self-administered questionnaire completed by participants and caregivers for information on recurrent falling. It is known that self-reported fall incidents are being under-reported (Peel, 2000; Mackenzie et al., 2006), a phenomenon potentially aggravated by apathy. If true, this might have led to an underestimation of the actual effect. Furthermore, apathy was assessed with the GDS-3A, which was validated in individuals from age 85 to 90 years (sensitivity 69% and specificity 85%) (van der Mast et al., 2008). We reckon that the GDS-3A is a rather crude measure that has not been validated in a similar age sample as the current study. In a recent study the GDS-3A in two home-dwelling populations (mean age 81.3 and 81.8 years respectively) appeared to have a high specificity but a low sensitivity (88.5–92.6% versus 29.3–32.8% respectively) (Bertens et al., 2016). A low sensitivity of the GDS-3A may have resulted in underestimation of the impact of apathy on recurrent falling due to misdiagnosing apathy, therewith strengthening our results. Finally, since we extract apathy items from the original GDS-15, it may be questionable to what extent the remaining GDS-12 remains a valid measure for depression. However, the GDS-15 was designed to measure a broad range of depressive symptoms. Whereas it cannot be used as a screening measure for depression (yes/no) after exclusion of three (apathy) items, in our opinion it still reflects the presence of depression symptomatology.

To conclude, the impact of apathy on (recurrent) falling may vary per age-group. Further investigation on the impact of apathy on (recurrent) falling is warranted using larger study samples and preferably a prospective study design. If results are consistent, more complete apprehension of apathy as a fall risk factor may help to compile more targeted interventions and may thereby help to reduce the burden of falls. By extension, we would recommend further research on the impact of apathy on intervention strategies for fall prevention. Many studies have been focusing on multidimensional intervention strategies for the prevention of falling (Gillespie et al., 2012). Among others, both home-based and group exercise programs have proven to be effective in reducing both rate of falls and risk of falling (Gillespie et al., 2012). However, factors such as low confidence in the rehabilitation program and lack of motivation led to non-adherence to exercise programs (Uzor et al., 2013). Considering the definition of apathy with lack of motivation as a core symptom, and the difficulty of maintaining exercise in the general population, it is very likely an individual with apathy is not easily motivated to participate in exercising programs. Given the above facts, perhaps group exercise programs should be preferred above home-based programs to prevent falls in persons with apathy. Furthermore, in community based older persons, with regard to maintaining exercise programs, motivational interviewing combined with guidance of a physical therapist has shown to be effective (Arkkukangas et al., 2017). Although modestly, in traumatic brain injury, motivational interviewing has been shown to help to maintain physical activity and even diminish apathy (Lane-Brown & Tate, 2009; Lane-Brown & Tate, 2010). Perhaps in older persons with apathy, motivational interviewing should be the strategy of choice in order to improve physical activity. The effect of motivational interviewing on completing exercise programs in older persons with apathy to prevent them from falling, has yet to be determined.

Finally, perhaps in older persons with apathy, physical activity should focus on for example, aerobics. Aerobics has shown to improve blood perfusion of the prefrontal cortex which plays a crucial role in the genesis of apathy (Cusso et al., 2016). However, research in this field is lacking.

5. Conclusion

In conclusion, this study has shown that apathy was associated with recurrent falling in geriatric patients aged 65 to 75 years old visiting a fall-clinic. If the relationship between recurrent falling and apathy proves to be causal, detecting and incorporating apathy in the strategy of approach to older fallers may improve multifactorial falls interventions. Therefore, further investigation, preferably in prospective cohorts and using more extensive measurements for apathy, is warranted.

Declarations of interest

None.

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Appendix A. Sensitivity analyses: results for logistic regression analysis of the presence of apathy and recurrent falling (≥2 and ≥3 falls in the past 12 months) stratified for age. Patients with missing data on MMSE-scores (*N* = 26) excluded from the analyses

		Age 65–75				Age 75+			
		N	OR	95% CI	*p*-Value	N	OR	95% CI	*p*-Value
Recurrent falling	Model A	104	3.1	(14–7.4)	0.007*	113	1.0	(0.5–2.1)	0.965
(≥2)	Model B[a]	99	3.7	(1.3–10.8)	0.016*	102	0.3	(0.3–1.6)	0.348
Recurrent falling	Model A	98	9.8	(3.1–13.8)	< 0.001*	100	1.3	(0.6–3.1)	0.492
(≥3)	Model B[b]	96	11.6	(3.1–42.8)	0.002*	96	0.8	(0.3–2.2)	0.710

Model A adjusted for gender Model B[a] adjusted model for gender, smoking, alcohol use, score on MMSE, score on GDS-12, Charlson comorbidity index, and visual impairment Model B[b] (RF ≥ 3) adjusted model for gender, score on MMSE, score on GDS-12, Charlson comorbidity index, and visual impairment *Significance level $p < 0.05$.

Appendix B. Sensitivity analyses: results for logistic regression analysis on apathy and recurrent falling (≥2 and ≥3 falls in the past 12 months) including intermediates Berg Balance Scale and physical activity. Patients with missing data on MMSE-scores (N = 26) excluded from the analyses

	Recurrent falling ≥ 2 falls				Recurrent falling ≥ 3 falls			
	N	OR	95%-CI	*p*-Value	N	OR	95%-CI	*P*-Value
Model A	217	1.7	(0.1–2.9)	0.073	200	3.1	(1.6–5.8)	0.001*
Model B	201	1.4	(0.7–2.6)	0.307[a]	196	2.7	(1.4–5.5)	0.005[b]*
Model C								
[a]Berg Balance Scale	171	1.2	(0.6–2.5)	0.631	165	2.3	(1.0–5.4)	0.510
[b]Physical activity	195	1.3	(0.7–2.5)	0.413	186	2.4	(1.2–4.9)	0.016

Model A adjusted for age and gender Model B[a] adjusted model for age, gender, smoking, alcohol use, score on MMSE, score on GDS-12, Charlson comorbidity index, visual impairment.
Model B[b] adjusted model for age, gender, score on MMSE, score on GDS-12, Charlson comorbidity index and visual impairment.
Model C[a+b]: Model B + intermediate Berg balance or physical activity * Significance level $p < 0.05$.

Appendix C. Sensitivity analyses: results for negative binomial regression analysis on apathy and number of falls. Patients with missing data on MMSE-scores (N = 26) excluded from the analyses

	IRR	95%CI	*p*-Value
Model A	2.55	1.83–3.56	< 0.001
Model B	1.59	1.10–2.31	0.014

Model A adjusted for age and gender.
Model B adjusted for age and gender, score on MMSE, score on GDS-12, smoking and alcohol use

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