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Review

Risk factors for apathy in Alzheimer's disease: A systematic review of longitudinal evidence

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ABSTRACT

Background: Apathy is frequent and persistent in Alzheimer's disease (AD), associated with poor prognosis and carer distress; yet our knowledge of risk factors remains limited.
Aims: To identify risk factors associated with apathy incidence and progression in AD over time.
Methods: We systematically reviewed evidence based on longitudinal studies assessing risk factors for apathy in AD up to June 2021. Two authors independently assessed article eligibility and rated quality.
Results: 13,280 articles were screened, of which 13 met inclusion criteria. Studies had a mean follow-up of 2.7 years reporting on a total of 2012 participants. Most findings were based on single studies of moderate quality evidence. Risk factors increasing apathy onset were: being a carrier of the T allele of the PRND gene polymorphism, and having high levels of the IL-6 and TNFα cytokines at baseline. Risk factors for apathy worsening were: reduced inferior-temporal cortical thickness, taking antidepressants, being an ApoE ε4 carrier, living longer with AD, lower cognitive test scores, higher baseline apathy, premorbid personality traits (lower agreeableness, higher neuroticism), and higher midlife motivational abilities.
Conclusions: Although results are limited by the small number of studies, this review identified specific genetic, neurobiological, AD specific, and dispositional factors that may increase risk of apathy onset and worsening in AD.

1. Introduction

Rather than being an isolated behavioural symptom, apathy in Alzheimer's disease (AD) is best conceptualized as a neuropsychiatric syndrome, characterized by a reduction of goal-directed behavior in several life areas, expressed by diminished motivation, interest, expression of emotions, and social interaction (Robert et al., 2018). Apathy is multidimensional in nature, as it has several domains - namely executive apathy, initiation apathy, and emotional apathy- giving different apathy profiles in individuals according to which domain is predominant in its expression (Radakovic and Abrahams, 2018).

Apathy is common and persistent in AD, with prevalence ranging from 45 % to 60 % (Leung et al., 2021). It is generally associated with a more severe clinical profile of AD, higher mortality and morbidity rates, greater functional and cognitive decline, greater depression, and diminished quality of life (Vilalta-Franch et al., 2013; Clarke et al., 2010; Starkstein et al., 2006; Nijsten et al., 2019). Moreover, apathy seems to be one of the most disrupting symptoms for carers of people with dementia, having a strong link with carer burden and also complicating disease management and care (Dauphinot et al., 2015; Nobis and

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Husain, 2018). Although several medications are used to treat apathy, evidence of their clinical effectiveness remains limited, and there are currently no treatments for improving or preventing apathy in AD (Theleritis et al., 2017; Manera et al., 2020). Understanding the causation of apathy and factors related to its progression is key for developing future effective treatment and prevention strategies.

Several frameworks and theoretical models have been proposed to understand the causation of apathy in AD. Studies investigating the neuroanatomy of apathy in AD have shown that apathy is associated with disrupted functioning of specific medial frontal brain structures -such as the ventral striatum, the anterior cingulate cortex, and the orbitofrontal cortex- areas implicated in the generation and control of voluntary actions (Le Heron et al., 2019). Neuroimaging data have also shown that apathy is associated with a reduction in cortical connectivity and grey matter volume of the medial and inferior-frontal cortex in AD (Theleritis et al., 2014; Lanctôt et al., 2017).

The relationship between different AD cerebrospinal fluid (CSF) biomarkers and apathy has also been investigated with inconclusive findings. For example, a recent literature review concluded that amyloid protein burden is a marker of apathy in early-stage AD, whereas tau protein burden is associated with higher apathy throughout AD progression (Lanctôt et al., 2017). While contradictorily, a longitudinal study examining the trajectory of apathy in a mixed sample of people with all type dementia over 5-years, have found that lower levels of CSF amyloid beta 1–42 ($A\beta_{1-42}$) are associated with increasing apathy over time, while higher levels of CSF total tau (t-tau) and phosphorylated tau (p-tau) are predictive of decreased levels of apathy over time (Banning et al., 2020). Similarly to CSF biomarkers, our understanding of the genetic contributions of apathy in AD is currently limited, with discrepancies reported in relation to whether apolipoprotein e4 (APOE e4) increases risk, and of the role of the catechol-o-methyltransferase gene, with one study identifying the latter as protective, and other studies finding no association (Lanctôt et al., 2017).

Despite theory and research advocating a strong neurobiological origin of apathy in AD (Sultzer et al., 2016; Gatchel et al., 2017) approximately 50% of people with AD do not manifest apathy, despite showing impairments related to neurodegeneration (Starkstein and Leentjens, 2008); thus, although many people with AD experience neurodegeneration on several brain structures associated with apathy, not all individuals will experience apathy. As a result, recent studies have conceptualized apathy as a syndrome that cannot solely be understood from a neurobiological perspective, and hypothesizing that other variables might be involved in its onset (Massimo et al., 2018). For example, a recent biopsychosocial model developed by Massimo et al. (2018) proposed both “direct” (neurodegeneration) and “indirect” (patient, caregiver, and environmental) factors that may be implicated in the onset and expression of apathy in AD. Neurodegeneration is thought to increase vulnerability to specific stressors, which may trigger apathy. Evidence-based patient factors include genetic risk (i.e. APOE e4 carriers), and dementia severity; while hypothesized factors are acute medical problems and unmet needs. Proposed environmental factors include lack of activity, overstimulation and understimulation (Massimo et al., 2018). Although promising, this model is based mostly on evidence from cross-sectional studies and is therefore limited in explaining who is more likely to be at risk of developing apathy in AD (Massimo et al., 2018).

We lack information on specific evidence-based variables related to apathy, that might guide research and clinical practice. Hence, the purpose of our study was to conduct the first systematic review of longitudinal evidence assessing all possible factors that increase the risk of apathy onset and worsening over time in AD. A secondary objective was to assess the quality of the evidence.

2. Methods

The protocol for this systematic review was registered at PROSPERO in June 2019; registration number: CRD42019139308.

2.1. Search strategy

The search strategy adhered to PRISMA guidelines (Moher et al., 2009) and was conducted in March 2019 and updated in June 2021. We searched four databases: MEDLINE, Embase, PsychINFO, and CINAHL using several search terms related to Alzheimer’s disease (i.e. AD, dement*), apathy (i.e. apath*, abulia), longitudinal studies (i.e. Cohort stud*, prospective), and risk factors (i.e. vulnerability, precipitating factors). The search strategy is presented in Appendix A. There was no publication date restriction, the language was limited to English and Spanish, and grey literature was also searched. Finally, we hand-searched the references of relevant reviews and articles to ensure no studies were missed.

2.2. Eligibility of studies

Inclusion criteria: a) longitudinal studies (retrospective, prospective and cohort studies); b) including participants with a diagnosis of AD of any severity; c) assessing the relationship between any predictive variable and apathy (as primary or secondary outcome) over time using a validated rating tool of apathy in AD. Exclusion criteria: Studies with a mixed sample of people with dementia that did not report separate data in people with AD.

2.3. Data extraction and analyses

All titles and abstracts of retrieved articles were screened by the primary author (IA), with four other authors (VO, PR, AB, and GM) independently screening 10 % of all retrieved articles at random. Full-text eligibility was performed by the primary author, with three authors randomly evaluating 20 % of those meeting inclusion criteria (VO, PR, AB). Disagreements were discussed with a third author. Data were extracted by IA using a data extraction form which included: details of the sample, study design, outcomes, confounders, follow-up rate, and relevant statistics (odds ratio, confidence interval, and p-values).

2.4. Quality assessment

Each study’s quality was independently assessed by two authors (IA and GM), and discrepancies resolved with a third author (VO). To assess quality and risk of bias of the prospective studies exploring risk factors for apathy, we combined items from the Newcastle-Ottawa Quality Assessment Scale (NOS) - adapted version for cohort studies (Wells et al., 2014), and from the Critical Appraisal Skills Programme (CASP) checklist for cohort studies. With this merged tool including items from the adapted NOS and CASP checklists, we rated each study on the following areas: 1. *Selection of sample*, which assessed representativeness of the sample, sample size, evidence of a power calculation, and if participants with apathy were excluded at baseline; 2. *Outcomes and confounders,* where we rated if a specific measure of apathy was used, whether standardized scales were used to measure other variables, and if the study addressed relevant confounders for risk factors; and 3. *Analyses and results*, which rated follow-up duration and rate, appropriateness of the statistical analyses and reporting of results (**see** Appendix B**)**.

3. Results

3.1. Search results

18,815 titles were identified with 17 additional studies identified through hand searching the references of included articles and relevant reviews. After removing duplicates, 13,281 titles remained, of which 13,132 were excluded. 149 articles were assessed for full-text eligibility, of which 13 studies met inclusion criteria. The search process is

presented in Fig. 1. Longitudinal studies addressing apathy incidence, prevalence or recurrence, but without data on risk factors were not included. A table of excluded studies is available in Appendix C. Due to heterogeneity of the risk factors identified we were unable to perform a meta-analysis.

3.2. Study characteristics

We identified three studies assessing risk factors for apathy onset in AD (Flirski et al., 2012; Holmes et al., 2011; Pocnet et al., 2013), of which all reported a risk odds ratio of apathy onset, and ten studies assessing risk for apathy worsening over time (Archer et al., 2007; Del Prete et al., 2009; Donovan et al., 2014; Dorey et al., 2020; Mortby et al., 2011; Rouch et al., 2019; Starkstein et al., 2010; Steinberg et al., 2014; Vogel et al., 2015; Wu et al., 2015). None of the studies investigating apathy worsening over time excluded people with apathy at baseline. Characteristics of the included studies are presented in Table 1.

3.3. Study design

Of the three studies assessing apathy onset, two were prospective (Flirski et al., 2012; Holmes et al., 2011), with a mean follow-up period of 1.6 years, and one was retrospective (Pocnet et al., 2013). Worsening of apathy over time was assessed by nine prospective studies, with a mean follow up period of 22 months, and by one retrospective study (Archer et al., 2007).

3.4. Sample characteristics

The total number of participants across studies was n = 2012. Two studies included people with mild to severe AD (Holmes et al., 2011; Archer et al., 2007) with the remaining eleven studies including people with mild to moderate AD. Twelve studies recruited people living in community settings, with the remaining study recruiting people living in long-term care (Archer et al., 2007). Five studies reported on a secondary analysis of a larger cohort study (Donovan et al., 2014; Dorey et al., 2020; Mortby et al., 2011; Steinberg et al., 2014; Vogel et al., 2015).

3.5. Apathy assessment

Eight studies assessed apathy as a primary outcome (Flirski et al., 2012; Holmes et al., 2011; Pocnet et al., 2013; Donovan et al., 2014; Mortby et al., 2011; Rouch et al., 2019; Starkstein et al., 2010; Steinberg et al., 2014), with the remaining five studies assessing apathy as a secondary outcome (Archer et al., 2007; Del Prete et al., 2009; Dorey et al., 2020; Vogel et al., 2015; Wu et al., 2015). Only one study (Starkstein et al., 2010) used an apathy-specific scale to measure apathy in AD, the Apathy Scale (Starkstein et al., 1992); with the remaining studies using the Neuropsychiatric Inventory (NPI) or NPI-questionnaire (NPI-Q) (Cummings et al., 1994).

3.6. Risk factors for apathy onset in AD

3.6.1. Genetic and neurobiological risk factors for apathy onset in AD

3.6.1.1. Genetic factors. In one study, carriers of the T allele of the Prion-like Protein Doppel gene 3' untranslated region (PRND 3'UTR) polymorphism were almost twice as likely to develop apathy compared to non-carriers (RR= 1.8; 95% CI 1.2–3.0, p = 0.02; n = 99) (Flirski et al., 2012). In the same study ApoE ε4, CYP rs754203, CYP i2 new polymorphism, Prion Protein (PRNP) gene codon 129 polymorphism, and PRND gene codons 26, 56 and 174 polymorphism status were not associated with increased risk of apathy onset (data not reported).

3.6.1.2. Infection-related inflammation markers. In one study, people with high levels of the pro-inflammatory serum cytokines tumor necrosis factor α (TNFα) and interleukin-6 (IL6), had two to three times increased risk of developing apathy (OR= 2.1, 95% CI 1.0–4.6, p = 0.06; and OR =2.9, 95% CI 1.3–6.6, p = 0.001 respectively) (Holmes et al., 2011).

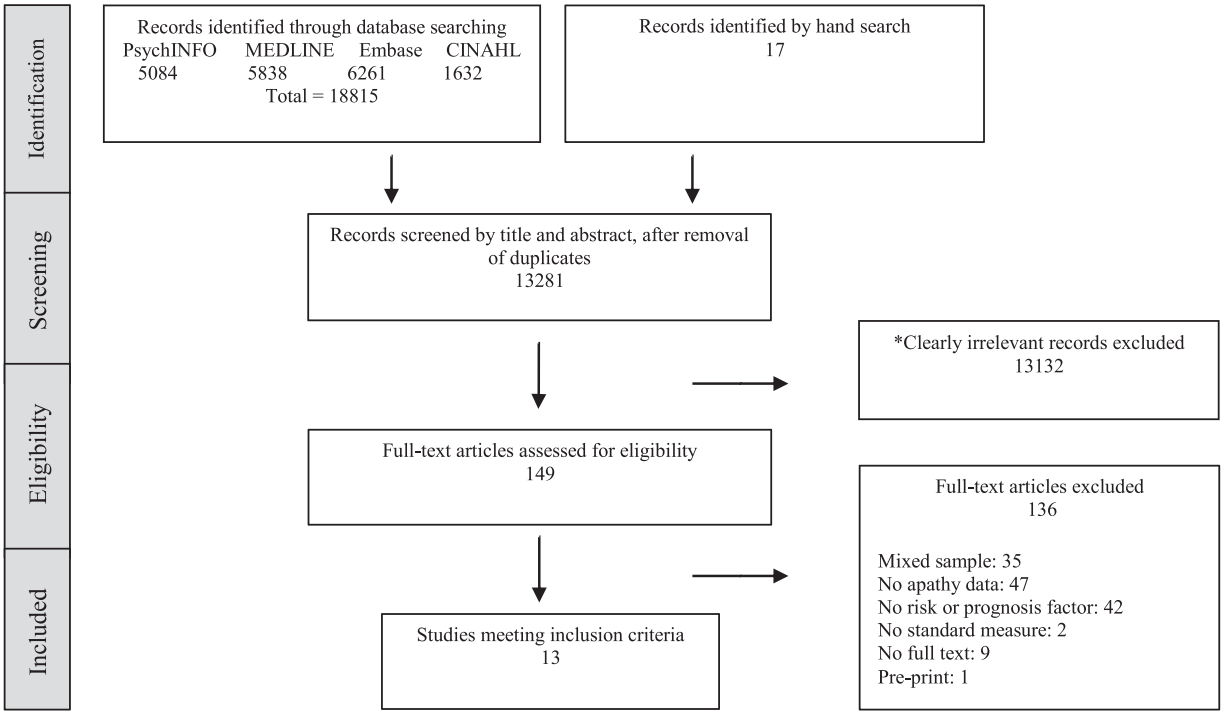

Fig. 1. prisma flow chart. Notes: * clearly irrelevant records: articles that weren't related to dementia but were identified due to the over inclusive search strategy; articles that didn't have a longitudinal study design, or explored apathy in other populations (i.e. apathy in adolescents or in animals).

Table 1
Descriptive characteristics of included studies.

Study	Sample N Mean age (SD) Severity MMSE/CDR	Follow up period	% at follow up	Apathy measure	Risk factor (s) assessed and Summary statistics	Confounders and controlled variables	Study findings	What was the primary outcome?
Studies that assessed risk factors for apathy onset								
Flirski et al. (2012) Poland.	Recruited from old age psychiatry academic departments. N = 99 Age: 76.6 (6.1) years. Mild AD: MMSE 19.6 (SD 4.6)	32.5 months (SD = 27.1)	64,6%	NPI	PRND gene 3' untranslated region (3'UTR) polymorphism. RR= 1.8; 95%CI= 1.2; 3.0, **p = 0.02**	APOE ε4 allele, age, sex	Being a carrier of the T allele of the 3'UTR PRND gene increased risk of apathy.	Behavioural and psychological symptoms.
Holmes et al. (2011) UK	Recruited from memory clinics. N = 275 Age: 82.7 (7.4) years Mild to severe AD: MMSE not reported	6 months	81%	NPI	High TNFα levels OR 2.1, 95%CI= 1.0;4.6, **p = 0.06** High IL6 levels OR = 2.9, 95%CI= 1.3;6.6, **p = 0.001**	Presence of delirium at follow-up, cognition (ADAS-Cog) Age, sex.	High levels of TNFα and IL6, increased risk of apathy.	Sickness behaviour symptoms.
Pocnet, C., et al. (2013) Switzerland.	Recruited from the Lausanne University Hospital Memory Clinic. N = 54 N control= 64 76.9 (8.5) years Mild AD MMSE 23.7 (SD 3.0)	Retrospective assessment	–	NPI	Premorbid personality (NEO-PI-R) Data not reported.	Age, current personality, cognition (IQCD), and ADLs.	Premorbid personality did not increase risk of apathy.	Behavioural and psychological symptoms.
Studies that assessed risk factors for worsening of apathy over time								
Archer et al. (2007) UK	Recruited from old age psychiatry services and nursing homes. N = 208 Age: 81.2 (6.4) years Mild to severe AD: MMSE 12.6 (SD 8.7)	Retrospective assessment	–	NPI	Premorbid agreeableness (NEO-FFI) r = 0.154; **p < 0.05**	Sex, age, age at AD onset, AD severity. Psychotropic medication	Low premorbid agreeableness associated with worsening of apathy.	Behavioural and psychological symptoms.
Del Prete et al. (2009) Italy	Outpatients recruited from AD units. N = 24 Age: 74.2 (8.2) years Mild AD: MMSE 18.3 (SD= 4.2)	1 year	100%	NPI	ApoE ε4 carriers **p < 0.001**	Onset of AD, pharmacological treatment for AD Nutritional status MMSE score.	Being an ε4 carriers increased risk of worsening of apathy.	Neuropsychiatric symptoms.
*Donovan et al. (2014) United States	ADNI database. N = 289 Age: 75.3 (7.5) years Mild AD; MMSE 23.3 (SD= 2.0)	3 years	100%	NPI-Q	Baseline cortical thickness (MRI) r = 0.44, r^2 = 0.20, df= 2823, **p < 0.0001** Baseline apathy (NPI-Q) β = 0.35, 95%CI= 0.29, 0.41, **p < 0.0001** Antidepressant use β = 0.08, 95%CI= 0.004, 0.15 **p = 0.04** Baseline disease duration (years) β = 0.04, 95%CI= 0.02, 0.06, **p < 0.0001** Baseline episodic memory (RAVLT)	APOE4, premorbid intelligence (AMNART-IQ) Age, sex	Reduced inferior-temporal cortical thickness at baseline, baseline apathy, antidepressant use, duration of AD (years), and low episodic memory and cognitive function at baseline predicted worsening of apathy over time. CSF biomarkers not predictive of worsening of apathy.	Apathy and hallucinations.

(*continued on next page*)

Table 1 (*continued*)

Study	Sample N Mean age (SD) Severity MMSE/CDR	Follow up period	% at follow up	Apathy measure	Risk factor (s) assessed and Summary statistics	Confounders and controlled variables	Study findings	What was the primary outcome?
					β = −0.006, 95%CI= −0.009, − 0.003, **p = 0.0001** Baseline cognition (WAIS-R Digit Symbol) β = −0.005, 95%CI= −0.008, − 0.003, **p < 0.0001** Baseline CSF ($A\beta_{1-42}$, t-tau, p-tau_{181p}) Data not reported.			
Dorey et al., (accepted 2019, in press) France	Sample from the PACO study; recruited from memory clinics. N = 187 Age: 79.4 (6.4) Mild AD: MMSE 24.6 (SD 2.4)	18 months	80%	NPI- Q short versión.	Neuroticism-volatility (NEO PI-R) β = 0.09, 95%CI= 0.01; 0.18, **p = 0,02** Neuroticism-withdrawal (NEO PI-R) β = 0.03, 95%CI= 0.05; 0.11 p = 0466	Age, sex, education, and MMSE at baseline.	Volatility domain of neuroticism increased risk of worse apathy over time.	Behavioural and psychological symptoms.
Mortby et al. (2011) Switzerland	Subsample from the ADAMS cohort. N total= 19 Age: 85.4 (5.9) Mild AD: MMSE 19.0 (SD 5.2)	18 months	100% DB	NPI	Midlife motivational abilities (O*NET estimate) F= 5.05, **p < 0.001**	Midlife cognitive abilities. Sex, ethnicity, marital status, and education.	High motivational abilities at midlife increased risk of worsening of apathy.	Apathy and depression.
Rouch et al. (2019) France	Recruited from memory clinics. N = 237 Age 79.4 (6.4) Mild AD: MMSE 24.5 (SD 2.5)	18 months	74%	NPI-Q, short version	Neuroticism (NEO PI-R) B= 0.007, 95%CI 0.003;0.011, **p = 0.002** Conscientiousness (NEO PI-R) B= −0.006, 95%CI − 0.011; − 0.001, **p = 0.02**	Sex, age, education, and baseline MMSE.	Higher levels of neuroticism increased apathy over time; higher levels of conscientiousness was associated with lower apathy.	Behavioural and psychological symptoms.
Study	**Sample N Mean age (SD) Severity MMSE/CDR**	**Follow up period**	**% at follow up**	**Apathy measure**	**Risk factor(s) assessed (measure) Summary statistics**	**Confounders and controlled variables**	**Study findings**	**What was the primary outcome?**
Starkstein et al. (2010) Argentina	Recruited patients from Dementia Clinics. N = 213 Age: 71.7 (7.1) Mild AD: MMSE 20.9 (SD= 5.5)	1–4 years	72%	Apathy Scale (AS)	Anosognosia at baseline (AQ-D) F= 10.6, **p = 0.001**	Baseline MMSE, depression and apathy. Age, sex, education, duration of AD.	Anosognosia at baseline was a significant predictor of more severe apathy over time.	Anosognosia and apathy.
Steinberg et al. (2014) USA	Sub-sample from the Cache County Study cohort. N = 327 Age: 84.23 (4.59) Mild AD: MMSE 21.97 (SD 4.59)	0.7–10.5 years	68% #	NPI	Atrial fibrillation, hypertension, diabetes mellitus (DM), angina, coronary artery bypass surgery, myocardial infarction, cerebrovascular accident, use of antihypertensive or DM medication. Data not reported.	Sex, educational level, APOE genotype, age at onset, and dementia duration	Vascular factors were not associated with apathy scores over time.	Neuropsychiatric symptoms.
Vogel et al. (2015) Denmark	Danish Alzheimer Intervention Study cohort; recruited from memory clinics, GPs, and	36 months	100%	NPI- Q	Awareness (Anosognosia Rating Scale) Data not reported.	Gender, age, and educational level.	Changes in awareness were not associated with apathy.	Awareness.

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Table 1 (*continued*)

Study	Sample N Mean age (SD) Severity MMSE/CDR	Follow up period	% at follow up	Apathy measure	Risk factor (s) assessed and Summary statistics	Confounders and controlled variables	Study findings	What was the primary outcome?
	psychiatry clinics Control group only N = 95 Age: 75.7 (6.3) Mild AD: MMSE 24.2 (SD 2.8)							
Wu, M.-K., et al. (2015) Taiwan	Recruited from neurology and memory clinics. N = 85 Age: 74.5 (8.8) Mild to moderate AD: MMSE 18.0 (SD 6.8)	18 months	100%	NPI	White matter tract integrity (fractional anisotropy) Data not reported.	Cerebrovascular risk biomarkers, and APOE genotypes. Age, MMSE	White matter tract integrity was not predictive of apathy scores over time.	Neurobehavioral symptoms.

Abbreviations: AD: Alzheimer's disease; ADAMS: Aging, Demographics, and Memory Study; AMNART-IQ: American National Adult Reading Test Intelligence quotient; AQ-D: Anosognosia Questionnaire for Dementia; β: partial regression coefficient estimate; CI: confidence interval; CSF: cerebrospinal fluid; df: degrees of freedom; F: F test statistic; GDS: Reisberg's Global Deterioration Scale; IL6: interleuquin-6; IQCD: Informant questionnaire on cognitive decline; MCI: mild cognitive impairment; MMSE: Mini Mental State Examination; MRI: magnetic resonance imaging; NA: not applicable; NEO-FFI: Five Factors Inventory; O*NET: Occupational Information Network; NEO PI-R: Personality Inventory-revised; NPI-Q: Neuropsychiatric Inventory brief questionnaire form; OR: Odd ratio; RAVLT: Rey Auditory Verbal Learning Test; RR: risk ratio; TNFα: tumor necrosis factor alpha; WAIS-R: Wechsler Adult Intelligence Scale-Revised. # Had at least one follow-up assessment. Significant associations ($p < 0.05$) in bold.

3.6.2. Premorbid personality traits

In one retrospective study (Pocnet et al., 2013), there was no significant association between apathy onset in AD and premorbid personality traits, measured by the Neuroticism-Extroversion-Openness (NEO) Personality Inventory (data not reported; n = 54). Table 2 presents an overview of all the risk factors assessed for apathy onset in AD across the three studies.

3.7. Risk factors for worsening of apathy over time

3.7.1. Genetic and neurobiological risk factors

3.7.1.1. Genetic factors. In one study, being an ApoE ε4 carrier increased risk of worsening of apathy compared to non-carriers ($p < 0.001$, no other data reported; n = 24) (Del Prete et al., 2009).

3.7.1.2. Neurodegeneration. One study found that reduced inferior-temporal cortical thickness at baseline predicted greater worsening of apathy over time ($r = 0.44$, $p < 0.0001$; n = 289) (Donovan et al., 2014). Wu et al. (2015) found that white matter tract integrity was not associated with worsening of apathy (data not reported; n = 85).

3.7.1.3. AD biomarkers. In one study amyloid beta 1–42 ($A\beta_{1-42}$), total tau protein (t-tau), or phospho-Tau 181 protein (p-tau 181p) did not predict apathy worsening over time (no data reported; n = 289) (Donovan et al., 2014).

3.7.2. Cardiovascular risk factors

Data from one study (Steinberg et al., 2014) showed that cardiovascular factors such as atrial fibrillation, hypertension, diabetes mellitus, angina, coronary artery bypass surgery, myocardial infarction, cerebrovascular accidents, use of diabetic/antihypertensive medication, were not related to apathy worsening over time (data not reported; n = 327).

3.7.3. Antidepressants, baseline apathy and premorbid personality

In one study, use of antidepressants at baseline was significantly associated with increased risk of apathy worsening (β = 0.08, 95% CI 0.004–0.15, p = 0.04; n = 289), while higher apathy at baseline was predictive of worse apathy over time (β = 0.35, 95% CI 0.29–0.41, $p < 0.0001$; n = 289) (Donovan et al., 2014).

Four studies assessed the association between premorbid personality traits and risk of apathy worsening (Archer et al., 2007; Dorey et al., 2020; Pocnet et al., 2013; Rouch et al., 2019). Archer et al. (2007), found that lower premorbid agreeableness increased risk ($r = 0.154$, $p < 0.05$; n = 208). In the study by Rouch et al. (2019) higher premorbid neuroticism was predictive of increased apathy (B= 0.007, 95% CI 0.003–0.011, p = 0.002; n = 237), whilst higher premorbid conscientiousness predicted lower apathy severity (B= −0.006, 95% CI

Table 2
Risk factors assessed for apathy onset in AD.

Risk factors assessed	Significant association	No significant association
Genetic and neurobiological		
Genetics	3'UTR PRND gene (Flirski et al., 2012)	APOE e4 carrier; CYP rs754203; CYPi2 * , PRNP 129 * , PRND 26, 56, 174 * . (Flirski et al., 2012)
Inflammation markers	Serum TNFα and IL6. (Holmes et al., 2011)	
Personality traits		Neuroticism, extroversion, openness (Pocnet et al., 2013)

Note: 3'UTR PRND: T allele of the Prion like Protein Doppel gene 3' untranslated region; APOE e4: apolipoprotein e4; * : polymorphism, PRNP: Prion Protein gene; TNFα: tumor necrosis factor alpha; IL6: interleukin 6.

−0.011to −0.001, p = 0.02; n = 237). Dorey et al. (2020) found that "volatility-neuroticism" increased risk of worsening of apathy (β = 0.09, 95% CI 0.01–0.18, p = 0,02; n = 187), whereas "withdrawal- neuroticism" did not (β = 0.03, 95% CI 0.05–0.11, p = 0466; n = 187). In one study (Mortby et al., 2011) higher premorbid midlife motivational abilities predicted greater worsening of apathy over time (F= 5.05, p < 0.001; n = 19).

3.7.4. Disease specific factors

Several disease specific factors were associated with increased worsening of apathy over time. These included living longer with AD (β = 0.04, 95% CI 0.02–0.06, p < 0.0001; n = 289), and scoring lower on baseline cognitive (WAIS-R Digit Symbol test) and episodic memory tests (Rey Auditory Verbal Learning Test) (β = −0.005, 95% CI −0.008 to 0.003, p < 0.0001; β = −0.006, 95% CI −0.009 to 0.003, p = 0.0001, respectively; n = 289) (Donovan et al., 2014).

3.7.4.1. Impaired awareness. Starkstein et al. (2010) found that impaired awareness at baseline was a predictor of worse apathy over time (F= 10.6, p = 0.001; n = 213), as measured by the Apathy Scale, whereas Vogel et al. (2015) found no significant association between baseline impaired awareness and apathy scores using the NPI-Q (no data reported; n = 95). Table 3 presents an overview of the identified factors for risk of apathy worsening.

Table 3
Overview of risk factors for apathy worsening over time in AD.

Risk factors for apathy worsening	Significant association	No significant association
Genetic and neurobiological		
Genetic	APOE e4 carrier (Del Prete et al., 2009)	
Neurodegeneration	Reduced inferior-temporal cortical thickness (Donovan et al., 2014)	White matter tract integrity (Wu et al., 2015)
AD biomarkers		Aβ 1–42, t-tau, and p-tau 181p (Donovan et al., 2014)
Cardiovascular		Atrial fibrillation, hypertension, diabetes, angina, coronary surgery, infarction, cerebrovascular accidents, diabetic/antihypertensive medication. (Steinberg et al., 2014)
Antidepressants	Use of antidepressants at baseline (Donovan et al., 2014)	
AD specific factors	Years living with AD, cognition, episodic memory, baseline apathy. (Donovan et al., 2014)	
	Impaired awareness (Starkstein et al., 2010)	Impaired awareness (Vogel et al., 2015)
Premorbid personality traits	Lower agreeableness(Archer et al., 2007)	Withdrawal- neuroticism (Dorey et al., 2020)
	Higher neuroticism, *higher conscientiousness (Rouch et al., 2019)	
	Volatility-neuroticism (Dorey et al., 2020)	
	Midlife motivational abilities (Mortby et al., 2011)	

Note: APOE e4: apolipoprotein e4; AD: Alzheimer's disease; Aβ 1–42: amyloid beta 1–42; t-tau: total tau protein; p-tau 181p: phospho-Tau 181 protein. * : negative association, meaning higher conscientiousness was linked with lower apathy.

3.8. Quality of studies

Of the thirteen included studies, ten were ranked to be of moderate quality (Flirski et al., 2012; Holmes et al., 2011; Archer et al., 2007; Del Prete et al., 2009; Donovan et al., 2014; Dorey et al., 2020; Mortby et al., 2011; Steinberg et al., 2014; Vogel et al., 2015; Wu et al., 2015) (mean score = 6.5), whereas two were rated as high-quality (Rouch et al., 2019; Starkstein et al., 2010) (mean score = 9), and one study as low quality (Pocnet et al., 2013) (score = 4). The overall mean score within studies was 6.7 out of 12. Lower quality ratings were mostly due to the use of a non-apathy specific scale to measure apathy, such as the NPI; not excluding participants with baseline apathy, and not reporting a power calculation. However, most of the studies had high scores in terms of controlling for potential confounders and secondary outcome assessment. Details of the quality assessment can be found in Appendix D.

4. Discussion

Identifying modifiable and non-modifiable risk factors related to apathy in AD is essential for preventing a more severe expression and progression of apathy, and improving disease prognosis. This systematic review is the first in the literature to identify and synthesise risk factors for apathy onset and worsening in AD as assessed by longitudinal studies.

Evidence from single studies suggests that carriers of the PRN 3'UTR polymorphism, and high inflammation markers serum cytokines IL6 and TNFα have an increased risk of apathy onset in AD (Flirski et al., 2012; Holmes et al., 2011, respectively). While being an ApoE ε4 carrier (Del Prete et al., 2009), having a reduced inferior-temporal cortical thickness (Donovan et al., 2014), AD-specific factors (years since AD diagnosis, declining episodic memory, and cognition) (Donovan et al., 2014), use of antidepressants (Donovan et al., 2014), and premorbid personality traits - higher neuroticism (Rouch et al., 2019) and volatility (Dorey et al., 2020), lower agreeableness (Archer et al., 2007), and higher midlife motivational abilities (Mortby et al., 2011)- were associated with worsening of apathy over time. There were conflicting findings in relation to impaired awareness (Starkstein et al., 2010; Vogel et al., 2015) and higher levels of premorbid conscientiousness was identified as a potential protective factor against apathy severity over time (Rouch et al., 2019).

We cannot acknowledge these findings as conclusive evidence, as most of the risk factors identified were assessed by individual studies, and overall, the quality of included studies was moderate. The limited number of studies identified (n = 13) and the heterogeneity of risk factors assessed prevented us from conducting a meta-analysis. Nevertheless, this systematic review is important as it is the first to systematically review longitudinal evidence on risk factors related to apathy in AD, highlighting the need for high-quality longitudinal research in the area.

4.1. Interpretation of results

4.1.1. Risk factors for apathy onset

The causation of apathy is widely studied from a neuropathological perspective, where neurodegeneration due to Alzheimer's disease and its underlying biomolecular mechanisms play a key role (Le Heron et al., 2019). Nonetheless, recent theoretical models propose that there may be direct factors (neurodegeneration) involved in apathy causation, and indirect factors (patient, caregiver, and environmental factors) that might act as triggers for apathy onset in AD (Massimo et al., 2018). We found limited longitudinal studies addressing direct or indirect factors for apathy, but we did however identify a previously unexplored genetic association for apathy onset; and one association between inflammatory cytokines and the occurrence of apathy. This latter association might give new information on systemic inflammation as a potentially indirect modifiable factor triggering apathy onset in AD.

4.1.1.1. Genes. We still lack precise specific genetic determinants for apathy in AD (Lanctôt et al., 2017). Yet, this review identified a novel genetic association investigated by Flirski et al. (2012), who found that carriers of the PRND 3'UTR polymorphism showed an elevated risk of developing apathy in AD. The PRND gene encodes the Dopell protein; its relationship with AD remains unknown, and the effect of its 3'UTR polymorphism have never been explored before (Flirski et al., 2012). This same study did not find any association with other genetic factors, such as the ApoE ε4 genotype. The association therefore between ApoE ε4 and apathy onset in AD remains inconclusive. For example, a previous longitudinal study showed that being an ApoE ε4 carrier is not associated with the onset of neuropsychiatric symptoms (NPS) in AD (Pritchard et al., 2007; study not included in this review as it didn't report information or data on apathy), while a cross-sectional study found a 2-fold increased risk of apathy for AD carriers of the ApoE ε4 genotype (D'Onofrio et al., 2011); suggesting that even though there is a correlation, so far, we can't assume causality between ApoE ε4 genotype and apathy, and that there might be other moderators or confounders involved. Data from our review indicates that the PRND 3'UTR polymorphism requires further exploration in order to assess its role as a marker of apathy onset in AD. Future studies should explore the key mechanisms underlying genetic risk factors and how alterations on protein-encoding may affect the motivational system and increase the risk of developing apathy or other NPS in AD.

4.1.1.2. Inflammatory cytokines. Data from one study identified that increases in systemic inflammation markers TNFα and IL6, were associated with apathy onset (Holmes et al., 2011). These findings suggest that apathy may be part of a "sickness behavior", which is understood as a coordinated behavioral response to systemic inflammation to preserve energy during acute inflammatory events, such as a respiratory or genitourinary infection (Holmes et al., 2011). Systemic inflammation due to infections in people with AD is common (Holmes et al., 2011), as is the association between infections and behavioral changes, such as delirium in clinical settings (Fong et al., 2009). But, to identify data regarding systemic inflammation as a potential marker for apathy onset in those living with AD is new. This aligns with the Massimo et al. (2018) hypothesis that acute infection is a possible factor indirectly triggering apathy. If apathy can be considered as a behavioral response to systemic inflammation, the next step for researchers is to assess whether apathy decreases once the inflammatory response is controlled. Appropriate management of systemic inflammation might therefore be considered as a potential modifiable risk factor for apathy onset.

4.1.2. Risk factors for apathy worsening over time

Apathy in AD tends to be progressive, with people presenting with more severe apathy in advanced dementia (Lanctôt et al., 2017); this maybe be partly explained by the underlying neuropathological origins of AD as a progressive disease. In this review, we identified several risk factors for apathy worsening that are shared amongst those living with AD, due to its genetic and neurobiological nature. But, interestingly, we also identified research suggesting that pre-morbid personality traits might lead to more severe apathy progression over time. Neither of these shared and dispositional risk factors are modifiable. Yet, we did find a dispositional risk factor; taking antidepressants, that could be considered as a potential modifiable risk factor for worsening of apathy over time.

4.1.2.1. Shared factors: genetics, neurobiological, and AD-specific risk factors. Being an ApoE ε4 carrier and greater baseline inferior-temporal cortical atrophy made an independent contribution to worsening apathy scores over time (Del Prete et al., 2009; Donovan et al., 2014). These findings are consistent with previous cross-sectional studies showing that the ApoE ε4 genotype is an independent risk factor for apathy progression (Monastero et al., 2006), and that inferior-temporal cortical atrophy correlates with higher apathy over time (Hahn et al., 2013; Agüera-Ortiz et al., 2015). This latter finding is coherent with the neurobiological framework for apathy in AD, where neurodegeneration is vital in understanding its causation (Le Heron et al., 2019). We did, however, find one study (Wu et al., 2015) reporting no significant longitudinal association between apathy and the integrity of twelve major white matter tracts related to neurodegeneration in AD. It is worth noting that this latter study was of low quality due to a small sample size. In contrast, a previous review including cross-sectional studies, supported the idea of white matter loss as a potential contributor to apathy (Lanctôt et al., 2017). We identified one study assessing AD biomarkers, which found no associations between $A\beta_{42}$, t-tau and p-tau and worsening of apathy (Donovan et al., 2014). These results are not in line with a recent high-quality longitudinal study including a sample of prodromal AD, where lower $A\beta_{42}$ was associated with an increase of apathy over time, while higher levels of t-tau and p-tau where related to a decrease in apathy (Banning et al., 2020). Further longitudinal studies are therefore needed to identify which specific genotypes, biomarkers, and brain structures are involved in apathy worsening over time in AD.

The study conducted by Donovan et al. (2014) investigated the contribution of disease-specific factors such as years living with a diagnosis of AD, baseline general cognition, and baseline episodic memory, and found that these factors were associated with worsening of apathy over time. The variables identified are related to dementia severity. Given that apathy is partially understood as the consequence of impaired neurological systems, it is plausible that living with the disease longer and experiencing more severe neurodegeneration would be associated with worsening apathy over time. This aligns with previous studies where apathy was cross-sectionally and longitudinally associated with dementia severity (Lanctôt et al., 2017; Wadsworth et al., 2012). Having higher apathy at baseline was also associated with worse apathy scores over time, indicating that apathy tends to be a progressive symptom.

Impaired awareness, a common feature of AD, was a significant predictor of apathy worsening in AD (Starkstein et al., 2010). One plausible explanation might be that people with better awareness of their limitations may actively seek to engage in activities to compensate for functional loss, which in turn would prevent them from experiencing higher levels of apathy. The opposite may occur when experiencing impaired awareness of their limitations, which may lead to withdrawal from activities and ultimately higher apathy (Starkstein et al., 2010). However, Vogel et al. (2015) did not find an association between impaired awareness and apathy. The latter study, as well as most of the included studies in this review, used the NPI to assess apathy; while the study that did find an association between impaired awareness and apathy used the Apathy Scale, which is a specific apathy tool validated in people with Alzheimer's disease (Starkstein et al., 2010), and was rated as high quality. These latter findings are in line with our recent systematic review on impaired awareness and affective symptoms in mild to moderate AD, where a positive association between apathy and impaired awareness in high-quality cross-sectional studies was found (Azocar et al., 2021).

4.1.2.2. Dispositional factors: premorbid personality and the use of antidepressants. Personality refers to stable differences in how people behave, feel, and think (Costa and McCrae, 1992). A recent review and metanalyses explored the influence of personality traits over dementia risk, finding robust associations with neuroticism and conscientiousness (Aschwanden et al., 2021); yet no similar associations have been gathered regarding the influence of personality traits over apathy in people living with AD. According to our review findings, worsening of apathy was related to higher premorbid neuroticism, higher premorbid volatility which is a subdomain of neuroticism, and lower premorbid agreeableness; while premorbid conscientiousness was a protective factor for experiencing less apathy over time. These findings suggest that

apathy might be, to some extent, an exacerbation of previous personality traits, as has been proposed for other NPS in AD (Zielin and McCabe, 2016). People with high levels of neuroticism may use more passive coping styles leading to higher levels of stress over time thus making them less able to cope with stressful events (Osborne et al., 2010), which could lead to higher vulnerability for experiencing apathy.

In relation to other individual characteristics, we identified one study that found high motivational abilities at midlife were predictive of greater worsening of apathy over time (Mortby et al., 2011). This association could be explained by 'unproductive persistence' where people with AD and high premorbid motivational abilities, when faced with challenges associated with AD, may become more vulnerable to experiencing higher levels of apathy (Mortby et al., 2011). The influence of premorbid personality characteristics over apathy in AD is an interesting and novel area of research; nonetheless, it requires the collection of retrospective data which may be prone to recall bias; therefore, interpretations and overall conclusion must be handled with caution.

Finally, one study reported a significant association between antidepressant use at baseline and higher apathy scores over time (Donovan et al., 2014). This finding aligns with longitudinal data showing that antidepressants may increase apathy in all-cause dementia (Gatchel et al., 2017). For example, Leontjevas et al. (2013) found that antidepressant treatment resulted in higher apathy levels in cross-sectional analyses. Antidepressants may be associated with changes at a neuromodulation level, affecting motivational systems related to apathy (Leontjevas et al., 2013). Depression and apathy in AD are distinct independent syndromes that share common symptomatology and are often misdiagnosed (Zhu et al., 2019). Hence, it might be possible that people with a misdiagnosis of depression, who are actually experiencing apathy, when prescribed antidepressants, could experience a worsening of their apathy symptoms. Although preliminary, the longitudinal association between antidepressant use and apathy worsening indicates caution when prescribing antidepressants in people with AD, especially within the context of their limited effectiveness for treating depression in dementia (Dudas et al., 2018). It is worth highlighting however that this longitudinal association between antidepressants and apathy is not conclusive, but rather a tentative finding based on a single study.

4.2. Limitations

Despite the significant strengths and originality of these findings, this review has several limitations. First, the small number of studies retrieved prevented meta-analyses and therefore, we cannot estimate risk for any of the factors identified. An important limitation of all but one of the included studies was the use of the NPI to measure apathy in AD. Although the NPI has shown good internal and external validity for apathy in AD, it is mostly used as a screening tool and it is not a comprehensive measurement for apathy. Moreover, the NPI is unable to address the multidimensional nature of apathy in AD (Radakovic et al., 2015); this not only gives uncomplete information about apathy profiles, but also may be linked to underestimation of apathy and inaccurate apathy data. Nonetheless, in most studies, it is worth noting that apathy was the primary outcome investigated within the cluster of all other possible NPS in AD. Therefore, it is reasonable that specific apathy measures were not implemented.

Only three studies assessed risk of apathy onset, and only two of these reported risk-specific statistics (risk ratio, odds ratio and corresponding CIs). The remaining ten studies assessing apathy worsening over time reported either correlations, regression analyses, or t-tests. Most importantly, nine of these latter studies did not report whether or not they excluded (from the analysis or the study) people who experienced apathy at baseline. This limitation is understandable if we consider that, unlike other NPS in AD, apathy is one of the most common and prevalent NPS from the early stages of the disease and we cannot therefore conclude that the risk factors measured at baseline were definitive determinants for apathy worsening.

Two studies had less than 50 CE participants, which could have hindered internal and external validity of the findings related to the influence of ApoE status and high motivational abilities at midlife as risk factors for apathy worsening over time (Del Prete et al., 2009; Mortby et al., 2011). Finally, we included two lower quality retrospective studies, both exploring pre-morbid personality traits as a determinant of apathy in AD and with conflicting findings. One of relatively small sample size (n = 54) did not find a significant association between any premorbid personality traits and apathy onset in AD (Pocnet et al., 2013); while the other with a larger sample size (n = 208) found a significant association between premorbid personality traits and apathy worsening (Archer et al., 2007).

4.3. Clinical implications and future research

This is the first systematic review to investigate evidence-based risk factors for apathy in AD, gathering and presenting important knowledge for clinical settings, and highlighting key literature gaps and methodological deficiencies in apathy research. As apathy is consistently associated with poor prognosis, decreased quality of life and higher levels of carer burden (Vilalta-Franch et al., 2013; Nobis and Husain, 2018), identifying its key risk factors is likely to improve disease prognosis and lead to better outcomes for people with AD. Our findings suggest that clinicians should ponder the potential impact of antidepressants on apathy progression, weighing up the potential risk for worsening of apathy in AD against the possible benefits for other dementia outcomes, such as improvements in global functioning or their potential neuroprotective role as demonstrated in AD models (Mowla et al., 2007; Wang et al., 2016). Professionals should also consider that acute systemic infection could be involved in triggering apathy onset. Identifying other potentially modifiable factors responsible for triggering or worsening apathy is crucial for future work on its prevention. We recommend future studies to further assess the impact of antidepressants on apathy worsening and identify which other personal, interpersonal and environmental factors may be related to apathy in AD. For example, as some cross-sectional data suggest that when the caregiver is someone other than the spouse the likelihood of having apathy increases more than four times (Clarke et al., 2008), future longitudinal studies could investigate how the relationship between the main caregiver and the person living with AD might impact apathy and vice versa over time. It is also of great importance in future apathy research to explicitly measure the complex multidomain nature of apathy, by using appropriate multidomain apathy scales (i.e. the Dimensional Apathy Scale). It would be particularly interesting to investigate if there might be specific risk factors for the different apathy domains (executive, initiation and emotional apathy) within the AD continuum.

4.4. Conclusions

High quality longitudinal literature regarding apathy and its risk factors in AD is very limited. Even though we cannot provide solid conclusions regarding causality or the direct influence of risk factors for apathy, we do present some important insights. According to our findings, the expression of apathy in AD is influenced mainly by biological factors, but, at the same time, shared variables common in those living with AD, such as impaired cognition and memory, and dispositional variables such as personality traits may also play a role. However, fewer research studies have investigated dispositional or behavioral factors that precede the individual's dementia and how these might influence the expression of apathy, as the general understanding of apathy in neurocognitive diseases such as AD, is predominantly from a neuropathological perspective. Similarly, longitudinal data regarding the influence of environmental factors, such as the type, quality, and time of social interaction, the amount of daily activities, the impact of the physical setting, or the influence of stimulation over apathy, are largely absent from the field.

Apathy is a very common feature of AD, which is an extremely common type of dementia, both with no cure. Therefore, due to its high prevalence and undesirable outcomes in those with AD, we encourage continued exploration of possible modifiable factors that could open up new treatment perspectives for apathy. Based on our findings, special attention should be paid to the potential secondary effects of antidepressants, and the impact of comorbidities such as systemic infections; yet it is important to acknowledge these findings were based on single studies and future large-scale longitudinal research is needed in order to confirm these associations. A better understanding of the key risk factors for apathy is fundamental for developing targeted interventions and integrated care; this could improve the quality of life of those with AD, offer a better disease prognosis, and protect carers from severer burden.

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Ignacia Azocar: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Penny Rapaport:** Methodology, Formal analysis, Writing – review & editing, Supervision. **Alexandra Burton:** Methodology, Formal analysis, Writing – review & editing, Supervision. **Georgia Meisel:** Formal analysis. **Vasiliki Orgeta:** Conceptualization, Methodology, Formal analysis, Writing – review & editing, Supervision.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2022.101672.

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