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Incidental findings on brain MRI of cognitively normal first-degree descendants of patients with Alzheimer's disease: a cross-sectional analysis from the ALFA (Alzheimer and Families) project

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ABSTRACT

Objectives: To describe the prevalence of brain MRI incidental findings (IF) in a cohort of cognitively normal first-degree descendants of patients with Alzheimer's disease (AD).

Design: Cross-sectional observational study.

Setting: All scans were obtained with a 3.0 T scanner. Scans were evaluated by a single neuroradiologist and IF recorded and categorised. The presence of white matter hyperintensities (WMH) was determined with the Fazekas scale and reported as relevant if ≥2.

Participants: 575 participants (45–75 years) underwent high-resolution structural brain MRI. Participants were cognitively normal and scored over the respective cut-off values in all the following neuropsychological tests: Mini-Mental State Examination (≥26), Memory Impairment Screen (≥6), Time Orientation Subtest of the Barcelona Test II (≥68), verbal semantic fluency (naming animals ≥12). Clinical Dementia Rating (CDR) had to be 0.

Results: 155 participants (27.0%) presented with at least one IF. Relevant WMH were present in 7.8% of the participants, and vascular abnormalities, cyst and brain volume loss in 10.7%, 3.1% and 6.9% of the study volunteers, respectively. Neoplastic brain findings were found in 2.4% of participants and within these, meningiomas were the most common (1.7%) and more frequently found in women. A positive correlation between increasing age and the presence of IF was found. Additionally, brain atrophy greater than that expected by age was significantly more prevalent in participants without a parental history of AD.

Conclusions: Brain MRIs of healthy middle-aged participants show a relatively high prevalence of IF even when study participants have been screened for subtle cognitive alterations. Most of our participants are first-degree descendants of patients with AD, and therefore these results are of special relevance for novel imaging studies in the context of AD prevention in cognitively healthy middle-aged participants.

Trial registration number: NCT02198586.

Strengths and limitations of this study

- Estimating the chance of discovering incidental findings (IF) helps clinicians and researchers to adequately inform and manage these situations.
- One hundred and fifty-five participants (27.0%), most of them cognitively normal first-degree descendants of patients with Alzheimer's disease (AD), presented with at least one IF.
- All images were reviewed by the same radiologist, thus maximising the homogeneity of the readings and reports.
- Our results are relevant for studies aimed at preventing AD in cognitively healthy middle-aged participants with increased risk of developing the disease.
- The generalisability of the results to the general population may be limited.

INTRODUCTION

MRI provides excellent spatial resolution and tissue characterisation without making use of ionising radiation. These advantages have spurred its use to image the brains of healthy individuals in clinical and research settings.[1 2] In these scans, it is not unusual to detect incidental findings (IF): unexpected abnormalities of potential clinical significance and unrelated to the purpose of the study. Estimating the chance of discovering IF is important to help clinicians and researchers to adequately

inform individuals and grant adequate access to standard medical care in order to manage these situations.[3] Therefore, in experimental protocols of human brain imaging research, it is important to anticipate the detection of IF and establish proper pathways for their management according to clinical and ethical considerations.[4 5]

The prevalence of IF reported in the literature shows a great variability as a function of several factors: the specific cohort characteristics, the image sequence in the MRI protocol (including whether contrast is used or not), the experience and number of image readers and the use of predefined analysis protocols and the postprocessing methodology of the images.[6 7] In a recent meta-analysis that included 19 559 participants aged between 11 and 63 years, an IF prevalence of 2.7% was found.[3] In particular, markers of cerebrovascular disease were excluded from this analysis. The authors concluded that IF prevalence increased with age and with higher resolution of the scans. In agreement, other studies in older populations have found significantly higher occurrences of IF. In observational studies, 32% (from a total of 700 participants, mean age 72.5 years),[7] 9.5% (from a total of 5800 participants with a mean age of 64.9 years)[8] and 77.9% (from a total of 503 participants with a mean age of 75.3 years)[9] of asymptomatic participants presented with IF. Therefore, IF are commonly revealed in neuroimaging research, but their occurrence greatly differs between study populations.

In addition to these factors, the discrepancy in the reported IF prevalence can also be accounted for by the definition of what constitutes a 'finding'. For example, white matter hyperintensities (WMH) are often reported as 'normal' findings in elderly individuals, since more than half of the healthy elderly population (>65 years old) has some degree of white matter lesions[10] and this proportion is even higher in individuals with vascular risk factors such as hypertension and diabetes.[11–13]

In this manuscript, we describe the prevalence of brain MRI IF in a cohort of 575 cognitively normal participants of the ALFA (for *Al*zheimer and *Fa*milies) study (Molinuevo *et al*. The ALFA project: a research platform to identify early pathophysiological features of Alzheimer's disease. Submitted). Current research supports that Alzheimer's disease (AD) pathology develops for several years before the onset of clinical symptoms.[14] The main goal of the ALFA study is to characterise the preclinical stage of AD and the most salient characteristic of this cohort is the elevated percentage of first-degree descendants of patients with AD. We compared the prevalence of IF in first-degree relatives of patients with AD versus non-relatives. Since familiar history is a common enrichment strategy for AD prevention trials (eg, PREVENT-Alzheimer programme;[15] the Adult children Study[16] and the Wisconsin Registry for Alzheimer's Prevention Program[17]), this might be of interest in the scope of novel studies aimed at preventing AD in cognitively healthy participants with increased risk of developing the disease (Molinuevo *et al*, Submitted).[1 18]

METHODS

Participants

The ALFA parent cohort, established by the Barcelonaβeta Brain Research Center (BBRC), is composed of 2743 cognitively healthy participants, mostly adult children of patients with AD, aged between 45 and 75 years, and was formed as a research platform from which to establish studies for the detection of factors indicative of AD in asymptomatic individuals (for a full description of the ALFA population, please refer to the Clinicaltrials.gov Identifier: NCT01835717 and ref. 19). ALFA participants were cognitively normal and scored over the respective cut-off values in all the following neuropsychological tests: Mini-Mental State Examination (≥26),[20] Memory Impairment Screen (≥6),[21] Time Orientation Subtest of the Barcelona Test II (≥68),[22] verbal semantic fluency (naming animals ≥12).[23] Clinical Dementia Rating (CDR) had to be 0.[24] All ALFA cohort participants were asked about their parental history of AD at baseline and categorised as family history positive (FH+) if they had at least one of their parents who had been diagnosed with AD before the age of 75. FH+ and FH− matched by sex and age groups were invited to participate in the present study (NCT02198586) which resulted in the inclusion of 608 individuals of the ALFA parent cohort that had no contraindications to brain MRI. Recruitment was initiated in April 2014 and finished in June 2015.

Ethical considerations

The MRI study protocol registered at Clinicaltrials.gov (Identifier: NCT02198586). It has been conducted in accordance with the directives of the Spanish Law 14/2007, of 3rd of July, on Biomedical Research (Ley 14/2007 de Investigación Biomédica). All participants accepted the study procedures by signing an informed consent form.

Brain MRI acquisition characteristics

Scans were obtained with a 3.0 T scanner (GE Discovery MR750 W 3T). The MRI protocol was identical for all participants and included high-resolution three-dimensional structural images weighted in T1 with an isotropic voxel size of 1 mm^3. The acquisition parameters were TR/TE/TI=8.0/3.7/450 ms, NSA=1, *flip angle*=8° and a matrix size of 256×256×160. In addition, three T2-weighted sequences (256×256, 1×1×3 mm matrix) were acquired: fluid attenuation inversion recovery (FLAIR: TR/TE/TI=11 000/90/2600 ms, *flip angle*=160°), fast spin echo (TR/TE=5000/85 ms, *flip angle*=110°) and gradient-recalled echo (GRE: TR/TE=1300/23 ms, *flip angle*=15°).

Radiological reporting

Scans were evaluated by the same trained neuroradiologist within the following week from MRI acquisition. All participants received the neuroradiological report of the MRI. An independent clinical consultant reviewed those

that contained IF and clinically relevant IF (eg, tumours, vascular abnormalities, WMH with comorbidities, cysts, chiari malformations, syringomyelia, ventriculomegaly suspicious of normal pressure hydrocephalus and encephalomalacia) were personally informed and participants referred for follow-up to the appropriate specialist (n=90/155). All individuals were offered a telephonic helpline should they present with additional questions or need further clarifications on the findings.

WMH were evaluated using the Fazekas scale,[25] a well-validated and established qualitative visual rating method, which separately categorises the severity of deep and periventricular lesions, on a scale from 0 to 3 (0: none or a single punctate WHM lesion, (1) multiple punctate lesions, (2) beginning confluency of lesions (bridging) and (3) large confluent lesions). WMH of Fazekas score ≥2 were reported as IF because, despite appearing in some normally functioning participants, these values are considered as relevant.[9 26 27] Brain volume loss was considered as IF by the radiologist when it was greater than that expected by age.

Statistical analyses

IF were categorised as WMH, vascular abnormalities (including lacunar infarcts, microhaemorrhages, aneurysms, cavernous malformations and malformations of venous development), cysts, neoplasias and others, including brain volume loss, and their prevalence calculated. The CIs were computed by Bayesian calculation. The effect of ageing in the most prevalent IF was assessed by means of a Pearson product-moment correlation coefficient (r). We also stratified participants into three different groups according to their age (between 45 and 54, between 55 and 64 and between 65 and 75). IF's prevalence per sex and age group was also quantified. The χ^2 test was used to assess for statistically significant differences in each most prevalent IF category between sexes and in brain atrophy and WMH between participants with or without a family history of AD. SPSS V.15.0 for Windows was used for all the statistical analyses. Differences were considered to be significant at $p<0.05$.

RESULTS

Six hundred and eight ALFA parent cohort participants were invited to take part in the present brain MRI study. Of these, 595 volunteers agreed to undergo MRI and 575 provided valid MRIs. Reasons that prevented MRI acquisition were claustrophobia (n=16), physical size or shape that precluded from lying in the scanner (n=3), and an imaging artefact caused by irremovable MRI-compatible metallic earrings (n=1). The main sociodemographic characteristics of the study participants and the results of the neuropsychological screening tests are shown in table 1. Out of the 575 individuals included in the study, 227 (39.5%) were men and 348 (60.5%) women, with a mean age of 58.2 and 57.5 years, respectively.

Prevalence of IF

One hundred and fifty-five (27.0% (95% CI 23.5% to 30.7%)) participants presented with at least one IF: 64 were men (mean age 57.7 years) and 91 women (mean age 57.8 years). Table 2 shows the prevalence of each IF.

With regard to WMH, 43 (7.4% (95% CI 5.6% to 9.9%)) individuals presented with a Fazekas 2 and 2 (0.3% (95% CI 0.1% to 1.2%)) with a Fazekas 3. Vascular abnormalities were present in 10.7% (95% CI 8.6% to 13.6%) of the study participants, the most prevalent being malformations of venous development (3.4% (95% CI 2.2% to 5.3%)) and lacunar infarcts (2.9% (95% CI 1.8% to 4.7%)) followed by single cavernous malformations (2.4% (95% CI 1.4% to 4.0%)) and microhaemorrhages (1.5% (95% CI 0.8% to 2.9%)). Cysts, including arachnoid and neuroepithelial ones, were found in 3.1% (95% CI 1.9% to 4.8%) of the cases. The prevalence of neoplasias was of 2.4% (95% CI 1.5% to 4.0%), whereas 10 participants (1.7% (95% CI 0.9% to 3.2%)) presented with a meningioma. Concerning other abnormalities, 7.0% (95% CI 5.1% to 9.3%) of the participants showed a brain volume loss greater than that expected by age and 1.0% (95% CI 0.5% to 2.2%) of them had a Chiari type I malformation. Finally, nine participants presented with extracerebral findings. Representative images of specific IF can be found in figure 1.

Table 1 Characteristics of the study population (N=575)

	Age, years (SD)	Women (%)	Education, years (SD)	Neuropsychological screening			
				MMSE	MIS	TO	SF
45–54 years (n=211)	49.8 (2.3)	60.53	14.2 (3.3)	29.2 (0.9)	7.9 (0.4)	70 (0.0)	23.4 (4.9)
55–64 years (n=245)	59.6 (2.8)	60.8	13.6 (3.6)	29.0 (1.1)	7.8 (0.5)	70 (0.0)	22.4 (5.3)
65–75 years (n=119)	68.3 (2.9)	56.7	12.9 (3.6)	28.8 (1.2)	7.6 (0.6)	70 (0.0)	21.2 (5.0)
Total (N=575)	58.6 (7.3)	57.8	13.6 (3.5)	29 (1.1)	7.7 (0.5)	70 (0.0)	22.5 (5.2)

MIS, Memory Impairment Screen; MMSE, Mini-Mental State Examination; SF, verbal Semantic Fluency (naming animals); TO, Time Orientation Subtest of the Barcelona Test II.

Table 2 Prevalence of incidental findings

Finding	n (%)	95% CI
White matter hyperintensities*	45 (7.83)	(5.9 to 10.3)
Vascular abnormalities		
Lacunar infarcts	17 (2.96)	(1.8 to 4.7)
Microhaemorrhages (n=9)		
Single (cortical/deep)	2 (0.35)/2 (0.35)	(0.10 to 1.24)/(0.10 to 1.24)
Various (cortical/deep)	4 (0.70)/1 (0.17)	(0.28 to 1.77)/(0.04 to 0.96)
Structural vascular abnormalities (n=36)		
Aneurysm	1 (0.17)	(0.04 to 0.96)
Cavernous malformation (single/various)	14 (2.43)/1 (0.17)	(1.466 to 4.04)/(0.04 to 0.96)
Malformation of venous development	20 (3.48)	(2.27 to 5.31)
Cysts		
Arachnoid (supratentorial/infratentorial)	3 (0.52)/5 (0.87)	(0.19 to 1.51)/(0.38 to 2.01)
Pineal†	2 (0.35)	(0.10 to 1.24)
Neuroepithelial	1 (0.17)	(0.04 to 0.96)
Choroidal fissure cyst	2 (0.35)	(0.10 to 1.24)
Posterior fossa cyst‡	4 (0.70)	(0.28 to 1.77)
Right hippocampus cyst	1 (0.17)	(0.04 to 0.96)
Neoplasias		
Meningioma	10 (1.74)	(0.95 to 3.16)
Pituitary mass	2 (0.35)	(0.10 to 1.24)
Small intraventricular mass§	1 (0.17)	(0.04 to 0.96)
Cerebellar hemispheric mass	1 (0.17)	(0.04 to 1.96)
Other abnormalities		
Brain volume loss¶ (n=40)		
Frontal	8 (1.39)	(0.71 to 2.71)
Temporal	8 (1.39)	(0.71 to 2.71)
Parietal	7 (1.22)	(0.60 to 2.48)
Cerebellum and brain stem	4 (0.69)	(0.28 to 1.77)
Diffuse loss of brain volume	13 (2.26)	(1.33 to 3.82)
Chiari malformation type I	6 (1.04)	(0.49 to 2.25)
Syringomyelia	1 (0.17)	(0.04 to 0.96)
Ventriculomegaly suspicious of NPH**	2 (0.35)	(0.10 to 1.24)
Non-specific focus of altered signal††	4 (0.52)	(0.28 to 1.77)
Extracerebral findings (n=9)		
Left frontal hyperostosis	1 (0.17)	(0.04 to 0.96)
Signal alterations of clivus	1 (0.17)	(0.04 to 0.96)
Other otorhinolaryngological processes‡‡	6 (1.04)	(0.49 to 2.25)
Right eye diameter increased	1 (0.17)	(0.04 to 0.96)
Encephalomalacia after traumatic brain injury	1 (0.17)	(0.04 to 0.96)

*Fazekas scale score ≥2.
†>1 cm in diameter.
‡Arachnoid cyst versus mega cisterna magna.
§Possible subependymoma.
¶Enlargement of the subarachnoid spaces and sulcus (bigger than that expected by age).
**Normal pressure hydrocephalus.
††Excluding white matter hyperintensities related to small vessel disease.
‡‡Excluding mild inflammatory disease (mucosal thickening or small retention cysts).

Age-specific distribution of IF

As a whole, a positive correlation between the prevalence of IF and increasing age was found (r=0.254, p<0.001). IF were more frequent in the 65–75 years old group (n=54, 45.4% (95% CI 36.7% to 54.3%)) than in the 55–64 years old (n=68, 27.8% (95% CI 22.5% to 33.7%)) and the 45–54 years old (n=33, 15.6% (95% CI 11.4% to 21.2%)) ones. Table 3 shows the age-specific distribution of the most frequent IF.

With regard to specific categories, a positive correlation was found between the incidence of relevant WMH (r=0.165, p<0.001), vascular abnormalities (r=0.125, p=0.003) and brain volume loss (r=0.358, p<0.001) with increasing age. Concerning vascular abnormalities, a statistically significant higher prevalence of both lacunar infarcts (r=0.116, p≤0.005) and microhaemorrhages (r=0.136, p=0.001) with increasing age was also found. With respect to brain volume loss, cortical atrophy

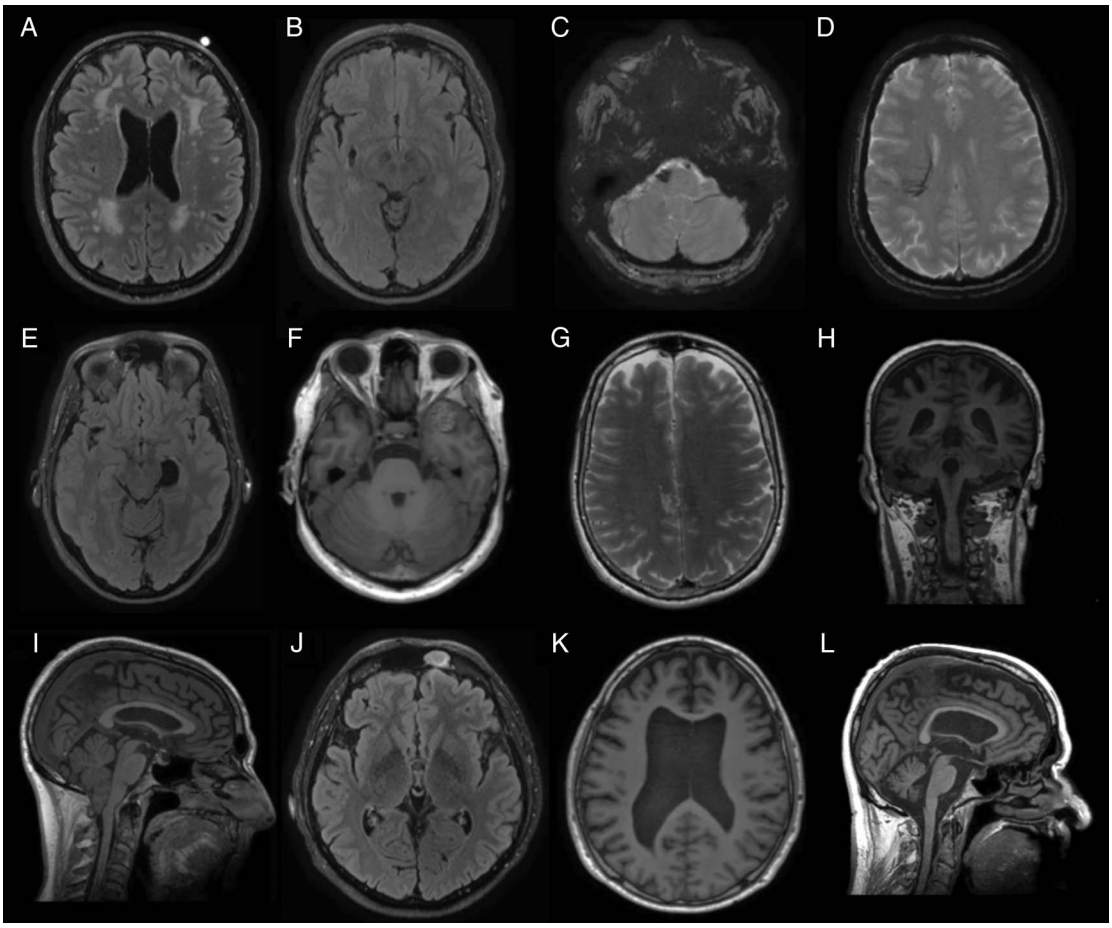

Figure 1 Incidental findings on brain MRI. (A) White matter hyperintensities. (B) Lacunar infarct. (C) Cavernous malformation. (D) Malformation of venous development. (E) Arachnoid cyst. (F) Meningioma. (G) Non-specific focus of altered signal. (H) Brain volume loss. (I) Chiari malformation type I. (J) Otorhinolaryngology process. (K) Ventriculomegaly suspicious of NPH. (L) Brain stem atrophy.

showed a positive correlation (r=0.240, p<0.001), whereas cerebellar and brain stem atrophies did not.

Sex-specific distribution of IF

We found no statistically significant differences between genders in the general prevalence of IF (p=0.589). Unexpected findings were found in 28.2% of the men and 26.1% of the women. When the most prevalent categories of IF were analysed, statistically significant differences between sexes were found in brain volume loss (p=0.039) that was more frequent in men (9.7% (95% CI 6.5% to 14.2%)) than women (5.2% (95% CI 3.3% to 8.0%)) and quasi-significant differences in neoplasias (p=0.051) that were more prevalent in women (4.3% (95% CI 2.6% to 6.9%)) than in men (1.3% (95% CI 0.5% to 3.8%)). Within neoplasias, meningiomas were more frequent in women (n=9 women, n=1 man). None of the other IF categories showed statistically significant differences between genders.

Family history of AD and prevalence of IF

As a whole, we found no statistically significant differences in the prevalence of IF between participants who had a family history of AD and those who did not (p=0.149). IF were found in the 24.9% (95% CI 20.8% to 29.6%) of participants with a positive family history of AD and the 30.5% (95% CI 24.6% to 37.0%) of individuals with no family history of AD. The prevalence of WMH (p=0.408) was not significantly different between volunteers with or without a family history. Unexpectedly, brain volume loss showed significant differences (p=0.005) between groups being more prevalent in the FH− group (table 4).

DISCUSSION

In this study, we aimed at describing the prevalence of IF from brain MRI in healthy participants aged between 45 and 75 of a population-based study, most of them first-degree descendants of patients with AD. The IF found were classified on the basis of their MRI characteristics alone and were not confirmed by further studies. IF were found in 27.0% of the participants, which is similar to studies involving older participants[7] and higher than the prevalence typically reported in most previous studies with comparable populations.[8]

Table 3 Age distribution of the most prevalent incidental findings

Finding	45–54 years (n=211)	95% CI	55–64 years (n=245)	95% CI	65–75 years (n=119)	95% CI
White matter hyperintensities, n (%)*	7 (3.32)	(1.64 to 6.68)	21 (8.57)	(5.68 to 12.75)	17 (14.29)	(9.13 to 21.71)
Vascular abnormalities*						
Lacunar infarct, n (%)*	2 (0.95)	(0.29 to 3.36)	6 (2.45)	(1.15 to 5.23)	8 (6.72)	(3.48 to 12.71)
Microhaemorrhage, n (%)*	0	–	5 (2.04)	(0.90 to 4.67)	4 (3.36)	(1.36 to 8.31)
Single cavernous malformation, n (%)	2 (0.95)	(0.29 to 3.36)	8 (3.26)	(1.6 to 6.30)	4 (3.36)	(1.36 to 8.31)
Malformation of venous development, n (%)	9 (4.26)	(2.28 to 7.90)	10 (4.08)	(2.25 to 7.37)	1 (0.84)	(0.20 to 4.55)
Neoplasias						
Meningioma, n (%)	3 (1.42)	(0.51 to 4.07)	5 (2.04)	(0.90 to 4.67)	2 (1.68)	(0.52 to 5.89)
Pituitary mass, n (%)	0	–	2 (0.82)	(0.25 to 2.90)	0	–
Small intraventricular mass,† n (%)	1 (0.47)	(0.11 to 2.60)	0	–	0	–
Cerebellar hemispheric mass, n (%)	0	–	1 (0.41)	(0.09 to 2.24)	0	–
Brain volume loss*						
Frontal, n (%)*	0	–	1 (0.41)	(0.90 to 2.24)	7 (5.88)	(2.92 to 11.64)
Temporal, n (%)*	2 (0.95)	(0.29 to 3.36)	2 (0.82)	(0.25 to 2.90)	4 (3.36)	(1.36 to 8.31)
Parietal, n (%)*	2 (0.95)	(0.29 to 3.36)	2 (0.82)	(0.25 to 2.90)	4 (3.36)	(1.36 to 8.31)
Cerebellum and brain stem, n (%)	1 (0.47)	(0.11 to 2.60)	1 (0.41)	(0.90 to 2.24)	2 (1.68)	(0.52 to 5.89)
Diffuse loss of brain volume, n (%)*	1 (0.47)	(0.11 to 2.60)	4 (1.63)	(0.66 to 4.11)	8 (6.72)	(3.48 to 12.71)

*Statistically significant positive correlation with increasing age (r, p<0.005).
†Possible subependymoma.

Nevertheless, some other papers report much higher prevalence rates.[9] These discrepancies can be mostly accounted for by the criteria for defining what constitutes an IF, technical features (type and quality of MRI sequences and the training of the scan reader)[13 28–30] and the characteristics of participants included (presence of comorbidities, screening selection and ethnicity).[28 29] For instance, in a retrospective study that included 1000 asymptomatic volunteers, only 18% of them presented with IF.[7] In comparison to our study, the age range of their population (3–83 years old) was wider including very young participants who are less prone to the present parenchyma atrophy or vascular pathology.

Overall, we found a positive correlation between the prevalence of IF and increasing age, while no sex-specific differences appeared significant. In addition to participant's age, the resolution of the MRIs used in previous studies was generally worse, thus reducing their capability of detecting microbleeds or small cavernomas. In general, a higher prevalence of IF is reported in studies using at least one high-resolution sequence.[8 9 13 30–33] A T2-weighted GRE facilitates the detection of haemorrhage, cerebral microbleeds and calcifications.[34] A T2-weighted sequence is especially sensitive in detecting infratentorial brain pathology; meanwhile, FLAIR is dedicated to identifying small vessel disease.[34] On the other hand, we did not use contrast-enhanced MRI. The absence of contrast is thought to leave some small lesions unnoticed,[6] and underestimate the prevalence of IF.[13]

Differences in the definition of IF also contribute to the variation of the reported IF prevalence among previous studies in the literature. In most of them,[8 13 28–30] the classification of IF was based on previous guidelines,[28] consisting of three categories as a function of their clinical relevance. In our case, we chose to categorise any structural finding discovered as an IF regardless of its clinical relevance. In this regard, other studies did not include WMH as an IF,[13 28 29] which were reported as age-related changes. However, we considered WMH with a Fazekas score ≥2 as IF, because they have been regarded as secondary to small vessel pathology by other authors.[25–27 35] WMH have important clinical and risk factor associations, underlining that they should not be ignored as inevitable 'silent' consequences of the physiological ageing of the brain.[36] In our study, 7.8% of the participants presented with relevant WMH (Fazekas score ≥2) and their prevalence significantly increased with advancing age. These results confirm previous findings where a 10-fold increase in the prevalence of WMH was found in participants older than 55, especially in those with risk factors for small vessel disease such as hypertension and diabetes.[3 11 13] Nevertheless, the prevalence of WMH in our study is lower than in other works evaluating IF in healthy individuals, most likely because those included older participants.[7 9 10 37]

Asymptomatic lacunar infarcts are frequently reported on imaging studies on elderly asymptomatic individuals.[34]

Our results are in agreement with previous studies reporting that lacunes are common IF in the brains of individuals in their 60s, and their prevalence as well as size increased with age.[9 38 39]

As far as brain volume loss is concerned, 7.0% of our study's participants presented with brain volume loss greater than that expected by age and its prevalence significantly increased with increasing age. One study involving older participants (73 years old) revealed a slightly higher brain volume loss prevalence (18%) than ours.[7] In this regard, it has to be noted that the inclusion criteria for our study were very strict in the definition of normal cognition. Therefore, participants with subclinical cognitive impairment may have been excluded from the study, thus resulting in a lower prevalence of cortical atrophies. Generally, brain volume loss is not considered an IF since it is relatively normal in the elderly.[3 28 30] However, we considered those with brain volume loss greater than that expected by age as an IF because their manifestation may reflect the presence of subclinical pathology. Indeed, it is known that the rate of progression of global and regional brain atrophy is associated with future cognitive deterioration and conversion to dementia.[40–42] Unexpectedly, individuals without a family history of AD showed a greater prevalence of abnormal brain atrophies for their age. However, this difference was driven by atrophies in the frontal lobe, and therefore it cannot be attributable to early AD pathology. In regions known to be affected by AD, such as the temporal and parietal cortices, no differences in atrophy prevalence were found between participants with and without a familiar history of AD.

With regard to gender-specific distribution of IF, statistically significant differences between genders were found in the prevalence of brain volume loss that was more frequent in men, and neoplasias that were more prevalent in women. Within the latter, and similarly to previous works,[3 7–9 13 28] meningiomas were the most common neoplastic brain finding (1.7%). The incidence of meningiomas has been reported to be about threefold higher in women, with the greatest difference observed between the ages of 30 and 59.[43] In our study, the higher prevalence of meningiomas found than in a previously reported study (0.9% in ref. 13) may be attributed to the use of MRIs of higher spatial resolution. Asymptomatic meningiomas require close clinical and radiological follow-up to rule out quickly enlarging tumours.[43]

Our sample was selected through a very accurate screening process to ensure that participants included were clinically and cognitively normal. Nevertheless, although Chiari malformations constituted an exclusion criterion, we found six participants who were unaware of harbouring them. Another strength of our study, which may lead to a higher reported prevalence, is that the MRI protocol was uniform for all participants and high-resolution MRI sequences were used. In addition, all images were reviewed by the same neuroradiologist, thus maximising the homogeneity of the readings and reports. Indeed, the experience of the reader is another factor that has an influence on the detection of IF.[13 29–34 44–46]

The strict recruitment criteria in the ALFA study may underlie the main limitation of this study in that the results reported here may not reflect the prevalence of IF in the general population. A greater percentage of our volunteers were first-degree descendants of patients with AD than what would be expected from the general population. Therefore, our prevalence estimates should not be regarded from an epidemiological perspective, but are of interest for design of AD prevention trials. Another limitation is the operationalisation of family history status as enrichment criteria for these trials. Ideally, family history should be supported by clinical records that might be difficult to access. In our cohort, 53% of the cases with a positive family history were backed up by confirmed medical records. On top of this, there is a certain arbitrariness in establishing a cut-off value in the age of AD onset in the index case to determine a positive family history status and selecting different threshold values may impact the observed prevalence estimates. In the ALFA cohort, this threshold is fixed at <75 years based on previous literature supporting that the age of AD onset in the index case needs to be limited as dementia occurring at a very old age is less likely to have a strong genetic component.[47 48] This 75-year-old limit has been used by us and other studies that combine multiple susceptibility *loci* into a global genetic risk score to improve the prediction of individuals at risk of suffering AD.[49]

There is still an open debate regarding the disclosure of IF to participants participating in imaging studies, since there is still a lack of evidence on which to base practice on the balance of harm versus benefit in telling research participants about findings.[5] The existing literature has evaluated the will of participants in medical and non-medical settings to be informed. In this respect, among study participants surveyed in the USA in 2005, 90% of 105 respondents said that they would to be informed of any IF, of whom 60% preferred this to be done by a physician in the research team.[50] In any case, further research to better understand the clinical and ethical implications of IF and their disclosure is needed for developing evidence-based policies for their management. In our study, volunteers were informed about our policy to disclose non-clinically relevant findings and agreed so by signing the study's informed consent form. All participants received a radiological report of their MRI (not just those presenting a finding (it being clinically relevant or not), but also those presenting no findings at all). A trained physician explained the findings to participants in order to provide clear information about their clinical relevance or lack of it. Clinically relevant findings were referred for specialist follow-up. Non-clinically relevant findings were also reported and volunteers were facilitated by a helpline should they have further questions or needed additional

Table 4 Distribution of the most prevalent incidental findings according to family history of AD

Finding	FH− (n=210)		FH+ (n=365)	
	n (%)	95% CI	n (%)	95% CI
White matter hyperintensities	19 (9.0)	(5.8 to 13.7)	26 (7.1)	(4.9 to 10.2)
Vascular abnormalities	19 (9.0)	(5.8 to 13.7)	41 (5.2)	(3.4 to 8.0)
Lacunar infarcts	7 (3.3)	(1.6 to 6.7)	10 (2.7)	(1.5 to 4.8)
Microhaemorrhage	5 (2.4)	(1.0 to 5.4)	4 (1.1)	(0.4 to 2.8)
Single cavernous malformation	3 (1.4)	(0.5 to 4.0)	11 (3.0)	(1.7 to 5.3)
Malformation of venous development	4 (1.9)	(0.7 to 4.8)	16 (4.4)	(2.7 to 7.0)
Neoplasia	6 (2.8)	(1.3 to 6.0)	8 (2.2)	(1.1 to 4.3)
Meningioma	3 (1.4)	(0.5 to 4.0)	7 (1.9)	(0.9 to 3.9)
Pituitary mass*	1 (0.5)	(0.1 to 2.6)	1 (0.3)	(0.0 to 1.5)
Small intraventricular mass*†	1 (0.5)	(0.1 to 2.6)	0	–
Cerebellar hemispheric mass*	1 (0.5)	(0.1 to 2.6)	0	–
Brain volume loss‡	22 (10.5)	(7.0 to 15.4)	18 (4.9)	(3.1 to 7.7)
Frontal*	6 (2.8)	(1.3 to 6.0)	2 (0.5)	(0.2 to 1.9)
Temporal	4 (1.9)	(0.7 to 4.8)	4 (1.1)	(0.4 to 2.8)
Parietal	4 (1.9)	(0.7 to 4.8)	3 (0.8)	(0.3 to 2.4)
Cerebellum and brain stem	2 (0.9)	(0.3 to 3.4)	2 (0.5)	(0.2 to 1.9)
Diffuse loss of brain volume	6 (2.8)	(1.3 to 6.0)	7 (1.9)	(0.9 to 3.9)

*Statistical analysis excluded due to small n.
†Possible subependymoma.
‡Finding a correlation with increasing age (r, p<0.05).
AD, Alzheimer's disease; FH+, mother and/or father who had been diagnosed with AD before the age of 75; FH−, mother and/or father who had not been diagnosed with AD before the age of 75.

clarifications. Even though we did not measure the psychological impact of disclosing non-clinically relevant findings, it is worth mentioning that out of the 65 events, none of them ever made use of this helpline. In general, we did not perceive any case in which disclosure caused any inconvenience: participants acknowledged the information and felt the feedback positively. Nevertheless, it would be interesting to investigate the psychological impact of knowing these findings on the quality of life of these participants.

In conclusion, we describe here that brain MRIs of healthy middle-aged participants show a relatively high prevalence of IF (27.0%) even after excluding individuals with subtle cognitive alterations. As a whole, a positive correlation between the prevalence of IF and increasing age was found and, within specific IF categories, relevant WMH, lacunes and brain volume loss prevalence significantly increased with age. Jointly, no significant differences between genders in the general prevalence of IF were found. However, brain volume loss was more frequent in men and neoplasias were more prevalent in women.

The main limitation of this study is the particular recruitment criteria in the ALFA project which argues against the generalisation of our data in the general population. In addition, the difficulty in establishing a cut-off value in the age of AD onset in the index case may have an impact on whether IF are more prevalent in first-degree relatives of patients with AD. Nevertheless, it is worth mentioning that most of our participants are first-degree descendants of patients with AD, and therefore the results presented here are of special relevance for novel imaging studies in the context of AD prevention in cognitively healthy middle-aged participants.

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