Potentially serious incidental findings on brain and body magnetic resonance imaging of apparently asymptomatic adults: systematic review and meta-analysis

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STRUCTURED ABSTRACT

Objectives

To 1) determine prevalence and types of potentially serious incidental findings on MRI in apparently asymptomatic adults, 2) describe factors associated with potentially serious incidental findings, and 3) summarise information on follow-up and final diagnoses.

Design

Systematic review and meta-analyses.

Data sources

Medline and Embase (inception to 25 April 2017), citation searches of relevant articles and authors' files.

Review methods

We included published studies reporting prevalence and types of incidental findings detected among apparently asymptomatic adults undergoing MRI of brain, thorax, abdomen or brain and body. We extracted data on study population and methods, prevalence and types of incidental findings, and final diagnoses. We estimated pooled prevalence using random effects meta-analysis, and heterogeneity using tau-squared statistics.

Main outcome measures

Prevalence of potentially serious incidental findings on MRI of brain, thorax, abdomen, and brain and body.

Results

Among 5,905 retrieved studies, 32 (0.5%) met the inclusion criteria (n=27,643 participants). Pooled prevalence of potentially serious incidental findings on brain and body MRI was: 3.9% (95% confidence interval [CI] 0.4 to 27.1%; brain 1.4% [95% CI 1.0 to 2.1%]; thorax 1.3% [95% CI 0.2 to

8.1%], abdomen 1.9% [95% CI 0.3 to 12.0%]); and 12.8% (95% CI 3.9 to 34.3%) when including incidental findings of uncertain potential seriousness, with generally substantial heterogeneity among included studies. Around half of potentially serious incidental findings were suspected malignancies (brain 0.6% [95% CI 0.4 to 0.9%]; thorax 0.6% [95% CI 0.1 to 3.1%]; abdomen 1.3% [95% CI 0.2 to 9.3%]; brain and body 2.3% [95% CI 0.3 to 15.4%]). There were few informative data on potential sources of between-study variation or factors associated with potentially serious incidental findings. Limited data suggested that relatively few potentially serious incidental findings had serious final diagnoses (48/234, 20.5%).

Conclusions

A substantial proportion of apparently asymptomatic adults will have potentially serious incidental findings on MRI, but little is known of their health consequences. Systematic, long-term follow-up studies are needed to better inform on these and the implications for policies on feedback of potentially serious incidental findings.

Systematic review registration

PROSPERO CRD42016029472.

WHAT THIS PAPER ADDS

What is already known on this topic

- Estimates of prevalence of incidental findings vary widely, and may be of limited value to practice as they often include non-serious incidental findings.
- Previous systematic reviews have focused on incidental findings detected on magnetic resonance imaging (MRI) of a single body region, patient populations undergoing MRI, or apparently asymptomatic people imaged using another modality.
- These estimates are not generalizable to brain and body MRI of apparently asymptomatic people, i.e. imaging which is increasingly conducted within large-scale imaging research and screening settings.

What this study adds

- In meta-analyses of published studies, pooled prevalence of potentially serious incidental findings on MRI of apparently asymptomatic people was 3.9% (1.4% brain, 1.3% thorax, 1.9% abdomen), and 12.8% (1.7% brain, 3.0% thorax, 4.5% abdomen) when including incidental findings of uncertain potential seriousness.
- Around half of potentially serious incidental findings were suspected malignancies.
- Limited follow-up data suggest that most potentially serious incidental findings may not be clinically serious on follow-up, and further research is needed.

INTRODUCTION

Brain and body (i.e. brain, thorax and abdomen) magnetic resonance imaging (MRI) is increasingly used for clinical and commercial screening and for research, with several large-scale population-based imaging initiatives ongoing around the world.[1-5] The detection of incidental findings unrelated to the purpose of the imaging[6] is an inevitable consequence. Clinicians and researchers should therefore anticipate incidental findings and develop appropriate policies for managing them, taking into account their expected prevalence and clinical severity.[7] Existing data on the prevalence of incidental findings from systematic reviews of MRI of a single body region,[8] patient populations undergoing MRI,[9] or apparently asymptomatic people imaged using another modality,[10] are not generalizable to brain and body MRI of apparently asymptomatic people (defined here as community-dwelling people not selected for imaging on the basis of symptoms, risk factors, or disease).

The clinical severity of incidental findings ranges from non-serious (e.g. simple renal cyst) to potentially life-threatening (e.g. some malignancies), but their nature and severity are often unclear. Diagnostic radiological imaging is tailored optimally to demonstrate (or exclude) pathologies relevant to a patient's presentation. By contrast, since incidental findings are, by definition, unrelated to the imaging's purpose,[6] no imaging protocol is specifically designed to optimize firm diagnoses of these. Further specific clinical follow-up is therefore often needed to permit final clinical diagnoses of incidental findings.

Given that knowing about clearly non-serious incidental findings would be of limited potential benefit, we focus here on 'potentially serious incidental findings', defined as those indicating the possibility of a condition which, if confirmed, would carry a real prospect of seriously threatening life span, or of having a substantial impact on major body functions or quality of life.[11] The development of well-informed approaches to the management of such potentially serious incidental findings on brain and body MRI in apparently asymptomatic adults requires data on their prevalence and types, factors associated with these, and on the resulting final diagnoses.

We therefore aimed systematically to review studies of brain, thorax, abdomen and of brain and body MRI to 1) determine the prevalence and types of potentially serious incidental findings among apparently asymptomatic adults, 2) describe factors associated with potentially serious incidental findings, and 3) determine what is known about the follow-up and final diagnoses of people with potentially serious incidental findings. This study was motivated by - and mainly conducted during preparations for - the ongoing UK Biobank multimodal imaging study (including brain and body MRI) of 100,000 people.[5]

METHODS

We registered the protocol for this review with PROSPERO,[12] and archived data online.[13]

Patient involvement

Patients were not involved in the development or design of this study.

Data sources

We searched Medline and Embase from inception to 25th April 2017 for references to studies in any language which reported the prevalence of incidental findings in apparently asymptomatic adults undergoing cardiac, abdominal or brain and body (i.e. brain and thorax and abdomen) MRI (Supplementary Methods 1). For brain MRI, we screened studies included in a published systematic review of incidental findings in apparently asymptomatic volunteers[8] and updated the search to 25th April 2017 (Supplementary Methods 1). We searched authors' files and forward and backward citations of retrieved studies for further relevant studies.

Study selection

One author (LG) screened all references for potentially eligible studies. A second author (LP) independently screened a random sample of 10% of references to assess the reliability of this process. Disagreements were resolved through discussion between these authors, with arbitration by a senior author (CLMS) if necessary. We retrieved full text articles of potentially eligible studies.

One author (LG) assessed articles for inclusion, and discussed uncertainties with a senior author (CLMS).

We defined apparently asymptomatic people as those who were not selected on the basis of any symptoms, risk factors, or disease, and who attended for population-based research imaging studies, commercial or occupational screening, or as research controls. We excluded studies of: patients (i.e. people selected for a study based on symptoms, risk factors or disease, or those admitted to or attending a health care facility for clinical diagnostic imaging); magnetic resonance angiography which only reported vascular incidental findings (due to limited generalizability); pre-specified subgroups of incidental findings (which would underestimate the prevalence of other incidental findings); children (<18 years old). We excluded studies which were not published in full. If multiple publications arose from a study, we prioritized the primary review question of prevalence, and included data from the largest cohort.

Data extraction

One author (LG) extracted data from all included studies on study population, study methods, and prevalence and types of all incidental findings using a pre-piloted, standardized data-extraction spreadsheet. To assess the reliability of this process, a second author (LP) independently extracted data from a 10% random sample of studies. Disagreements were resolved through discussion between these authors.

Study and population characteristics

We extracted data on: sample size; numbers of men and women; mean age and age range of participants; country in which the imaging was conducted (or, if this was not reported, the country of the first author's institution); body region(s) imaged; imaging setting (classified as either research [if participants were imaged during research studies], or non-research settings [imaging was performed in other contexts, including occupational imaging, or commercial imaging]).

Study imaging and IF reporting methods

We extracted data on: whether prevalence of incidental findings was assessed by reviewing MR images or reports; the specialist field and number of those reporting images; blinding of reporters to information about the participants; the MRI sequences performed; the dates that MRI was performed.

Data on IFs

We extracted data on: the total number of participants with incidental findings, the total number of incidental findings, or both if available; the number of participants with multiple incidental findings; the prevalence of incidental findings by age, sex, imaging sequence, reporter or any other factor assessed for association with incidental findings; all available data on follow-up investigations, treatment and final diagnoses for studies in which all participants with incidental findings or a specified subtype or severity of incidental findings were followed-up systematically.

Classification of incidental findings and final diagnoses

To determine which incidental findings were potentially serious according to our definition,[11] we referred to a list of potentially serious and non-serious incidental findings developed by UK Biobank, based on consultations with radiologists, published literature and the German National Cohort's methods[14] (Supplementary Methods 2). For any incidental finding not on this list, we directly applied our definition of a potentially serious incidental finding; where there was insufficient published information to apply our definition, we used study definitions of severe incidental findings, accepting that these vary somewhat between studies.[13] We sub-classified potentially serious incidental findings as suspected malignancy (e.g. masses), non-malignant, or possible indicators of malignancy (incidental findings which were not masses, but could be related to malignancy, e.g. pleural effusions [Supplementary Methods 3]). We classified final diagnoses as serious if they were likely to significantly threaten lifespan or have a major impact on quality of life or major body functions, and not serious if this was not the case. We described incidental findings or final diagnoses that could not be classified as 'indeterminate.'

Risk of bias assessment

In the absence of a validated quality assessment tool for studies of the prevalence of incidental findings, we extracted data on study characteristics which may influence risk of bias (sample selection methods, blinding of reporters to information about the participants, the specialty and number of image readers, and whether data on incidental findings were generated from reads of images or extracted from reports), and planned to consider their potential influence on the results through a series of subgroup analyses.

Data synthesis

We meta-analysed studies with a random effects model,[15] using maximum likelihood estimation methods[16] and modelling within-study variance as binomial, to calculate pooled prevalence of potentially serious incidental findings, and of suspected malignant incidental findings, separately for MRI of brain, thorax, abdomen, and brain and body. For the pooled estimates, we calculated both 95% confidence intervals (CI) and 95% prediction intervals; the latter indicate the range of true prevalence values expected in future studies.[17] We used t-scores (rather than the usual z score) to calculate 95% CIs, generating conservative estimates and allowing comparison with our prediction intervals (which also use t-scores). We included region-specific data from studies of brain and body MRI in the brain, thoracic and abdominal MRI meta-analyses. We derived data on thoracic incidental findings from studies of either cardiac or brain and body MRI or both. To obtain upper estimates of the prevalence of potentially serious incidental findings and of suspected malignant incidental findings, we performed sensitivity meta-analyses by adding the indeterminate incidental findings to the potentially serious incidental findings, and possible indicators of malignancy to the suspected malignant incidental findings. We calculated 95% CIs for individual studies' prevalence estimates using Clopper Pearson exact methods. We assessed statistical heterogeneity using tau-squared statistics, which provide a logit scale measure of between-study variance, represented in a more readily interpretable way by the 95% prediction intervals. We initially considered all study-level characteristics as potential candidates for subgroup analyses to explore reasons for heterogeneity of the prevalence of potentially serious incidental findings. However, we chose not to conduct subgroup analyses that were likely to be un-informative (e.g. due to missing data for a large proportion of studies or substantial imbalance in subgroup sizes).

We performed subgroup analyses by including study characteristics as covariates in the meta-analyses.[18] We decided not to perform formal statistical tests for possible publication bias since their application is limited in meta-analyses where outcome is expressed as a proportion.[19 20] We further decided not to conduct formal meta-analysis of data on the percentage of potentially serious incidental findings that resulted in serious final diagnoses (i.e., the positive predictive value of potentially serious incidental findings), to avoid undue emphasis on the limited data available. Instead, we described available findings and calculated a rough estimate of this percentage by summing numerators and denominators across the few studies with relevant data.

We used Microsoft Excel 2013 for descriptive statistical analyses, StatsDirect 3.0.177 for calculating 95% CIs for individual studies, and SAS 9.4 PROC NLMIXED (www.sas.com) for meta-analyses.

We obtained all data for this study from existing publications, and so did not need ethical approval.

RESULTS

Two authors agreed on 99% of the duplicate screened reference selections, and 100% of the duplicate extracted data.

Included studies

We included 32 studies[21-52] of 27,643 participants (range 2 to 5,800 participants, mean/median age range 21 to 75 years, 14,037/27,643 [50.8%] male) imaged between 1985 and 2016 (Supplementary Figure 1, Supplementary Table 1). These 32 studies comprised eight of brain and body MRI,[21-28] 22 of brain MRI,[29-50] and two of cardiac MRI.[51 52] No abdomen-only studies were identified (Supplementary Table 1).

Studies were performed in Europe (20 studies,[21-25 27-29 31 34 36 37 39-41 43 44 47 48 52] 17,702 participants), North America (six studies,[30 35 38 46 50 51] 5,789 participants), Asia (four studies,[26 32 33 45] 3,576 participants), and Australia (two studies,[42 49] 576 participants) (Supplementary Table 1). All but three assessed images for incidental findings; one assessed imaging reports,[49] and two did not report on this.[32 47] All studies involved radiologists, except one in which a cardiologist reported incidental findings on cardiac MRI (Supplementary Table 1);[52] in two studies, radiologists were involved in confirming incidental findings detected by others (trained readers [defined as researchers with training to doctor of medicine-level or training in neuropsychiatry] in one study[29] and MRI scan operators [not further defined] in another).[45]

Imaging sequences

The vast majority of participants were imaged using scanners of 1.5T or less (19 studies, 23,809/27,643 [86.1%] participants).[21-25 27 29-34 36 37 41 42 48 49 51] However, seven studies (1,556/27,643 [5.6%] participants) used 3.0T scanners,[26 28 39 40 43 50 52] two studies (370/27,643 [1.3%] participants) used 1.5T in some participants and 3.0T in others,[44 45] and four studies (1,908/27,643 [6.9%] participants) did not report magnet strength (Supplementary Table 2).[35 38 46 47] All but three brain MRI studies[23 36 47] used T1-weighted imaging; one of these used T1-weighted imaging in an unknown subset of participants.[40] Of the ten thoracic MRI studies, eight used non-

contrast whole thorax imaging (n=4817),[21-28] and five used cardiac-specific sequences (n=4099).[21 22 24 51 52] All abdominal MRI studies used T1-weighted imaging (Supplementary Table 2).

Risk of bias assessment

Only one study appeared to have imaged an unselected, random population sample (n=2500).[21] The majority of the remainder imaged selected samples or did not clearly report sampling methods. At least one radiologist reported all images in almost all studies; 14 studies (8199/27,643 [29.7%] participants)[21-24,26-28 33 34 37 43 46 48 51] had more than one reader for each set of images (Supplementary Table 1). Data on blinding of readers to participants' characteristics were incomplete, with only 16 studies (19,617/27,643 [71.0%] participants)[21 23 24 27 29-31 34 36-38 41 44 45 48 49] clearly reporting blinding of image readers to participant characteristics (Supplementary Table 1). There were no direct within-study comparisons of radiologist versus non-radiologist readers, of single versus multiple readers, or of blinding versus non-blinding of readers to participants' characteristics to reliably inform on any potential biases such methods may have on the prevalence of potentially serious incidental findings.

Prevalence and types of potentially serious incidental findings

Although 14 studies[21 24 25 27 31 32 34 36-38 41 43 50 51] reported data on multiple incidental findings per participant, none provided the number of participants with >1 potentially serious incidental finding, or data to enable calculations of this. We therefore based prevalence estimates on the assumption that no participant had >1 potentially serious incidental finding, recognizing that a very small number of participants may have more than one. The pooled prevalences of potentially serious incidental findings on brain, thoracic, abdominal and brain and body MRI were 1.4% (95% CI 1.0 to 2.1%), 1.3% (95% CI 0.2 to 8.1%), 1.9% (95% CI 0.3 to 12.0%) and 3.9% (95% CI 0.4 to 27.1%) respectively. When indeterminate incidental findings were included, pooled prevalence estimates increased to 1.7% (95% CI 1.1 to 2.6%), 3.0% (95% CI 0.8 to 11.3%), 4.5% (95% CI 1.5 to 12.9%) and 12.8% (95% CI 3.9 to 34.3%) respectively. Study-specific prevalence estimates ranged widely, with correspondingly wide prediction intervals, and tau-squared values ranging from 0.8 to 5.7

(indicative of substantial variance between studies) (Figure 1 and 2, Supplementary Figure 2, Supplementary Table 3).

Across body regions, suspected malignancies were the most common types of potentially serious incidental findings (accounting for roughly half of all such findings), with vascular findings also common on brain MRI (Figure 3 and Supplementary Table 4a-c). Pooled prevalences of suspected malignant potentially serious incidental findings were: brain 0.6% (95% CI 0.4 to 0.9%; thorax 0.6% (95% CI 0.1 to 3.1%); abdomen 1.3% (95% CI 0.2 to 9.3%); and brain and body 2.3% (95% CI 0.3 to 15.4%). When possible indicators of malignancy were included, these were 0.6% (95% CI 0.4 to 0.9%), 1.0% (95% CI 0.2 to 5.4%), 1.6% (95% CI 0.2 to 10.9%) and 3.0% (95% CI 0.4 to 20.4%) respectively (Supplementary Figure 2).

Subgroup analyses

Examination of the available data (Supplementary Tables 1 and 2) showed that several potential subgroup analyses would be uninformative due to very imbalanced subgroups or non-reporting of the relevant data for a large subset of studies. One or both of these reasons precluded subgroup analyses with respect to magnet strength (almost all 1.5T), contrast use (incomplete data), data source (almost all studies used images rather than reports of these), image reader specialty (almost all studies had reporting by radiologists), and sample selection method (only one study randomly selected participants).[21] We did not conduct subgroup analyses by: age or sex, because we did not have individual participant data to allow meaningful comparisons; study country, since there was no clear a priori reason for variation in potentially serious incidental finding prevalence by country; or body region because studies of brain and body MRI contributed data on different body regions from the same participants, violating the assumption that data within different subgroups are independent. We conducted brain and body and region-specific MRI subgroup analyses for imaging setting (research versus non-research) and for several factors which may inform on risks of bias (blinding of readers to participant characteristics and number of image readers) where sufficient data allowed. There was no evidence of any clinically meaningful or

statistically significant difference in prevalence of potentially serious incidental findings following the inclusion of subgroups as covariates (Supplementary Figures 3a-i, Supplementary Table 5).

Study-specific reports of factors associated with potentially serious incidental findings

Eight studies reported factors associated with potentially serious incidental findings,[25 27 29 30 34 36 39 42] while a further five reported factors associated with incidental findings requiring follow-up, which we considered an approximate proxy for potentially serious incidental findings (Supplementary Tables 6a-c).[33 37 43 46 52] Two studies found significant associations between incidental findings requiring follow-up and increasing age,[43 46] while a further two studies found a consistently higher prevalence of incidental findings requiring follow-up[33] and cavernomata[39] in older age groups, albeit not statistically significant (Supplementary Table 6a). There was no clear variation in prevalence of potentially serious incidental findings by sex (Supplementary Table 6b). Too few data were available on other factors (including medical history, symptoms, lifestyle factors and genetics) to demonstrate any clear associations with potentially serious incidental findings (Supplementary Table 6c). No data were available on the associations between imaging sequence or reporter specialty with prevalence of potentially serious incidental findings.

Follow-up and final diagnoses

Only five studies systematically followed-up and reported data on the final clinical diagnoses of selected subsets of participants with incidental findings (total number of such participants followed up = 234), representing 1.4 to 18.2% of all imaged participants in these studies (Table 1).[25,26,27 29,37] Summing arithmetically across these studies, overall only 48 of these 234 participants (i.e. about one fifth) had clinically serious final diagnoses (although half had indeterminate final diagnoses, mostly from one study of brain MRI,[29] in which participants were managed under ‘wait and see’ policies). No study reported follow-up in a manner which enabled enumeration of the clinical assessments (e.g. further imaging examinations, specialty referrals, biopsies etc.) performed to clarify final diagnoses.

Table 1: Methods of follow-up of 234 people with potentially serious incidental findings and severity of their final diagnoses

Study variables			Methods of follow-up of incidental findings			Severity of final diagnoses (n)		
First author surname and year of publication	**Imaged body regions**	**n followed-up/ N total imaged (%)**	**Subset of participants followed-up[a]**	**Data type (source)**	**Duration of follow-up**	**Serious**	**Non-serious**	**Indeterminate**
Bos 2016[29]	Brain	188/5800 (3.2)	All those with an incidental finding who were referred to specialists[b]	Clinical management (medical records)	Until last clinical follow-up or death	39	34	115
Sandeman 2013[37]	Brain	10/700 (1.4)	All those with an incidental finding who were referred to family doctors[c]	Resulting action (medical records)	-	5	5	0
Morin 2009[25]	Brain and body	5/148 (3.4)	All those with highly significant findings[d]	Investigations and treatments (contact with general practitioner or participant)	-	0	3	2
Lo 2008[26]	Brain and body	24/132 (18.2)	All those with an incidental finding which required further work-up[e]	-	-	4	20	0
Saya 2017[27]	Brain and body	7/44 (15.9)	All with incidental findings deemed to require follow-up[f]	Investigations (-)	-	0	7	0
Total n (% of 234 followed up)			.	.	.	48 (20.5)	69 (29.5)	117 (50)

- = not specified, . = not applicable

a. This could be considered as a study-specific proxy for potentially serious incidental findings but is not identical to the consistent definition that we applied in meta-analyses of prevalence of PSIFs. Hence study-specific n here differs from study specific numbers of PSIFs in meta-analyses.

b. Decision for referral depended on the incidental finding and consultation with clinicians.

c. Decision for referral depended on discussion between radiologists and a geriatrician and other clinicians as necessary.
d. Highly significant findings were defined as those requiring prompt medical follow-up, such as indeterminate masses in solid organs, enlarged lymph nodes and ovarian masses/cysts, as judged by consensus of two radiologists. Participants' family doctors were informed of the finding.
e. Definition of incidental findings requiring further work-up, or processes for judging this are not reported.
f. As determined by study radiologists, follow-up was discussed by a multi-disciplinary team including principle investigators, radiologists and other study staff (not otherwise specified).

DISCUSSION

Principle findings

We performed meta-analyses of published studies of the prevalence of potentially serious incidental findings among apparently asymptomatic adults undergoing MRI of brain, thorax, abdomen or brain and body. The pooled prevalence of potentially serious incidental findings was 3.9% (1.4% brain, 1.3% thorax, 1.9% abdomen). When additionally including incidental findings of uncertain potential seriousness, the pooled prevalence increased to 12.8% (1.7% brain, 3.0% thorax, 4.5% abdomen). There was wide variation among studies in their prevalence estimates, likely reflecting variation between studies in participants' characteristics, imaging setting, sample selection methods, and methods of detecting incidental findings, as well as the challenges of applying a consistent definition of potentially serious incidental findings to the available descriptions of incidental findings in published papers. Suspected malignant incidental findings accounted for around half of all potentially serious incidental findings on brain, thoracic, abdominal and brain and body MRI (0.6%, 0.6%, 1.3% and 2.3% respectively). The very limited systematic follow-up data available (mainly from brain MRI studies) demonstrated that only about 1/5 people with a potentially serious incidental finding had a serious final clinical diagnosis.

Strengths and limitations of this study

By including all identified published data on the prevalence of potentially serious incidental findings on brain, thoracic, abdominal and brain and body MRI, and by applying as consistent as possible a definition of potentially serious incidental findings across studies, we have provided data on the prevalence of those incidental findings which may have an important impact on health. This is the first review to include data on potentially serious incidental findings from different body regions, enabling comparisons of prevalence between regions. As such, our results are informative to people undergoing, or staff conducting, brain and body or region-specific MRI in apparently asymptomatic adult volunteers. As most studies comprised selected apparently asymptomatic populations, our results are directly applicable to imaging performed for research and non-research settings such as screening.

While we have not shown evidence of a statistically significant difference in the prevalence of potentially serious incidental findings between body regions, the pooled point prevalences were generally higher on abdomen MRI, and on brain and body MRI compared to either brain or thorax MRI, particularly so when indeterminate findings were included in sensitivity analyses. This pattern is biologically plausible and was also seen in data from some primary studies[21 25 26 28 53]. It is possible that the heterogeneity between included studies, the relative rarity of potentially serious incidental findings, methods of meta-analyses and conservative calculation of confidence intervals may have obscured true differences in the prevalence of potentially serious incidental findings between regions. Results on incidental findings from ongoing large population-based imaging studies (including the UK Biobank imaging sub-study, which by late August 2018 had imaged >27,000 of an intended 100,000 participants) should be able to confirm or refute this pattern in future.[5 14 54 55]

There was no evidence of any meaningful differences in the prevalence of potentially serious incidental findings between studies conducted in research or imaging settings for any body region, or between studies using readers blinded to participant characteristics versus not blinded or not stated, or for brain MRI studies using one versus >1 reader. Further subgroup analyses which may inform on factors influencing variation in prevalence in different body regions were limited, as data on relevant variables were either lacking for a large subset of studies, or resulted in very imbalanced subgroups.

Data were included in the review after screening and extraction by one, rather than multiple authors. While this may limit the accuracy of the data extraction, it is unlikely to have substantially impacted on our results given the very good agreement with a second reviewer on a 10% subset of the studies. Due to the lack of data on the participants with >1 potentially serious incidental finding, prevalence estimates were based on the assumption that only one potentially serious incidental finding occurs per participant; however, it is unlikely that a substantial proportion of participants had >1 potentially serious incidental finding. The prevalence of incidental findings deemed

'potentially serious' may vary with opinion and over time as evidence of their natural history accrues.

We could not explore the influence of technical imaging factors (e.g. image resolution, magnet strength) on the prevalence of potentially serious incidental findings, due to limited data availability and reporting consistency, but these are unlikely to substantially influence the detection of the most common potentially serious incidental findings (suspected malignancies and aneurysms). The vast majority of included studies involved systematic radiologist reviews of images to detect incidental findings. No study directly compared radiologist to non-radiologist readers, although other policies to detect incidental findings may produce very different results, such as radiographer flagging of concerning examinations for a radiologist to review.[55]

Comparison with other studies

A recently published umbrella review of incidental findings arising from a range of imaging modalities (including MRI) found no existing systematic reviews of the prevalence of incidental findings in apparently asymptomatic volunteers on cardiac, abdominal or brain and body MRI for comparison with our findings.[56]

Our update of an existing systematic review by Morris et al.[8] of incidental findings on brain MRI resulted in similar prevalence of suspected malignant incidental findings. The aforementioned recent umbrella review reported a prevalence of incidental findings on brain MRI of 22% (95% CI 14 to 31%), around ten times higher than our pooled prevalence estimate for brain MRI.[8 56 57] The majority of this difference is likely to be due to the umbrella review's inclusion of all reported incidental findings, regardless of their potential clinical significance, whereas we focused on potentially serious incidental findings. Some of the difference may also be due to different study inclusion criteria (reflecting the different focus of the umbrella review, which had broader inclusion criteria, including studies of patients as well as apparently asymptomatic people), as well as a difference in meta-analytic methodologies. Prevalence data, as proportions, will have a binomial distribution. The umbrella review used an arcsine transformation in its analyses of prevalence data,

which avoids the challenge of directly modelling binomial data, whereas we used an exact method, which does model the within-study variance as binomial to generate unbiased estimates.[16]
The recent umbrella review also reported far more final diagnosis data from studies derived from Morris et al. than we have here.[56] In order to calculate the proportion of incidental findings resulting in known final diagnoses, the participants who form the denominator should all undergo systematic follow-up in order to generate an accurate numerator. We therefore scrutinised reports of all our included studies and found that only five reported such systematic methods; we did not consider diagnosis data from other studies to be robust, since they may represent suspected, rather than final diagnoses.

Implications of this study

Apparently asymptomatic people may undergo brain and body MRI by participating in research, or access non-research MRI via referral from a doctor,[28] or directly[28 32 33] (e.g. as part of occupational screening,[31] private health insurance,[23] or company health care programmes[24 28]). Our prevalence data could be used to inform consent for MRI in both research and non-research settings. Such data could also help researchers calculate anticipated numbers of participants with potentially serious incidental findings in future studies, to inform the design of appropriate incidental findings handling policies.

Our review highlights the limited data available on the follow-up and final diagnoses of potentially serious incidental findings. Such data would inform judgements about the benefits versus harms of feeding back potentially serious incidental findings, an issue which warrants further investigation with systematic, long-term follow-up of participants with potentially serious incidental findings. Unlike public health screening programmes, which fulfill specific criteria to ensure net benefit,[58] identification of a potentially serious incidental finding does not always lead to detection of disease at a stage where intervention will confer benefit. Many potentially serious incidental findings will turn out to be clinically non-serious, but require potentially anxiety-provoking follow-up and potentially uncomfortable or harmful investigations to discover this. Even for those potentially

serious incidental findings that do turn out to be clinically serious, for most there is no clear evidence base to inform decisions about treatment, and early treatment of some disorders may confer harm.[59] Our prevalence data could inform power calculations for future clinical trials of conservative or active treatments of potentially serious incidental findings, in order to develop good medical practices which minimize harm to people with potentially serious incidental findings, and ensure appropriate use of health services.

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DATA SHARING STATEMENT

The full dataset is available at http://dx.doi.org/10.7488/ds/2100 with open access.

OTHER STATEMENTS

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: Dr. Gibson reports grants from Wellcome Trust, during the conduct of the study, and personal fees from UK Biobank, outside the submitted work; Professor Sudlow is Chief Scientist of UK Biobank; the remaining authors have no financial relationships with any organisations that might have an interest in the submitted work in the previous three years or other relationships or activities that could appear to have influenced the submitted work**.**

Contributors and guarantor

Dr Lorna M Gibson designed and conducted the study, collected, managed, analyzed and interpreted data, and prepared, reviewed and approved the manuscript.

Dr Laura Paul collected data, and reviewed and approved the manuscript.

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Professor Cathie LM Sudlow designed and supervised the study, interpreted data, reviewed, approved and decided to submit the manuscript for publication.

Professor Cathie LM Sudlow is the guarantor.

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Transparency declaration

Prof. Cathie LM Sudlow (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethical approval

We obtained all data for this study from existing publications, and so did not need ethical approval.

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Role of the study sponsors

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Statement of independence of researchers from funders

All authors are independent from the funders.

Patient involvement

Patients were not involved in the development or design of this study. The results of this study will be disseminated to the public by the investigators where possible.

Author access to data

All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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FIGURE TITLES AND LEGENDS

Figure 1
Title: Forest plots of the per-study prevalence and pooled prevalence estimates of potentially serious incidental findings, and of potentially serious incidental findings plus indeterminate incidental findings, detected on brain magnetic resonance imaging (MRI)

Legend:

CI= confidence interval

Tau-squared is an estimate of between-study variance on the logit scale. Zero represents no variance, and increasing values of tau-squared indicate increasing heterogeneity.

Blue = Per-study point prevalence and pooled prevalence estimate of potentially serious incidental findings on brain MRI

Orange = Sensitivity analyses which include incidental findings classified as indeterminate in the per-study point prevalence and pooled prevalence estimate of potentially serious incidental findings on brain MRI. Details of the types and numbers of potentially serious incidental findings are provided in Figure 3 and Supplementary Table 3a, while details of indeterminate findings are available online.[13]

a. We excluded 138 vascular incidental findings detected in six studies that used MR angiography,[24 31-34 38] from pooled analyses.

Figure 2
Title: Forest plots of the per-study prevalence and pooled prevalence estimates of potentially serious incidental findings, and of potentially serious incidental findings plus indeterminate incidental findings, detected on thoracic, abdominal and brain and body magnetic resonance imaging (MRI)

Legend:

CI= confidence interval

Tau-squared is an estimate of between-study variance on the logit scale. Zero represents no variance, and increasing values of tau-squared indicate increasing heterogeneity.

Blue = Per-study point prevalence and pooled prevalence estimate of potentially serious incidental findings on thoracic, abdominal and brain and body MRI

Orange = Sensitivity analyses which include incidental findings classified as indeterminate in the per-study point prevalence and pooled prevalence estimate of potentially serious incidental findings on thoracic, abdominal and brain and body MRI. Details of the types and numbers of potentially serious incidental findings are provided in Figure 3 and Supplementary Tables 3b-c, while details of indeterminate findings are available online.[13]

a. We excluded 200 incidental findings detected in studies that used specialist imaging sequences (97 breast lesions in a study including MR mammography,[21] 87 colonic polyps in two studies which included MR colonography,[22 24] 15 vascular findings such as stenosis or plaque in four studies which included MR angiography,[21 22 24 28] and one myocardial infarction in a study which included post-contrast cardiac imaging[24]) from pooled analyses.

Figure 3
Title: Numbers and types of potentially serious incidental findings on magnetic resonance imaging (MRI) by body region

Legend:

Further details of the types of potentially serious incidental findings are provided in Supplementary Tables 3a-c. We sub-classified potentially serious incidental findings as suspected malignancy (e.g. masses), possible indicators of malignancy (IFs which were not masses, but could be related to malignancy, e.g. pleural effusions) or non-malignant (Supplementary Methods 3). For the purposes of this figure, potentially serious incidental findings which were not suspected malignancies, possible indicators of malignancies, or suspected vascular findings were grouped as ‘suspected other.’