

MR imaging of the brain in large cohort studies: feasibility report of the population- and patient-based BiDirect study

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Abstract

Objectives To describe the implementation and protocol of cerebral magnetic resonance imaging (MRI) in the longitudinal BiDirect study and to report rates of study participation as well as management of incidental findings.

Methods Data came from the BiDirect study that investigates the relationship between depression and arteriosclerosis and comprises 2258 participants in three cohorts: 999 patients with depression, 347 patients with manifest cardiovascular disease (CVD) and 912 population-based controls. The study program includes MRI of the brain. Reasons for non-participation were systematically collected. Incidental findings were categorized and disclosed according to clinical relevance.

Results At baseline 2176 participants were offered MRI, of whom 1453 (67 %) completed it. Reasons for non-participation differed according to cohort, age and gender with

controls showing the highest participation rate of 79 %. Patient cohorts had higher refusal rates and CVD patients a high prevalence of contraindications. In the first follow-up examination 69 % of participating subjects completed MRI.

Incidental findings were disclosed to 246 participants (17 %). The majority of incidental findings were extensive white matter hyperintensities requiring further diagnostic work-up.

Conclusions Knowledge about subjects and sensible definition of incidental findings are crucial for large-scale imaging projects. Our data offer practical and concrete information for the design of future studies.

Key points

- Willingness to participate in MRI is generally high, also in follow-up examinations.
- Rates of refusal and prevalence of contraindications differ according to subject characteristics.
- Extensive white matter hyperintensities considerably increase the disclosure rates of incidental findings.
- MRI workflow requires continuous case-by-case handling by an interdisciplinary team.

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Keywords Magnetic resonance imaging · Cohort studies · Refusal to participate · Contraindications · Incidental findings

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Abbreviations

BL	Baseline
CI	Contraindication
CVD	Cardiovascular disease
fMRI	Functional magnetic resonance imaging
FU	Follow-up
IF	Incidental finding
MRI	Magnetic resonance imaging
OR	Odds ratio

rs-fMRI	Resting-state functional magnetic resonance imaging
WMH	White matter hyperintensity

Introduction

Magnetic resonance imaging (MRI) of the brain is increasingly used as part of large population-based studies [1–4]. In addition, patient cohort studies, recruiting large numbers of individuals with specific conditions like cerebral small vessel disease, symptomatic atherosclerotic disease or depression, often apply MRI in their examinations [5–8].

The implementation of standardised MRI into a study protocol is associated with additional financial, ethical and procedural challenges, especially in studies with large sample sizes. Depending on the specific research questions and study population, these include sample size calculations, standardisation and quality-assuring procedures as well as interdisciplinary management of incidental findings (IFs). Given this methodological complexity, publications of study-specific imaging protocols or reports on the prevalence of IFs are increasing [2, 9]. However, information on the willingness to participate or the nature and frequencies of contraindications (CIs) as well as the communication strategy of IFs are still sparse.

Willingness to participate and prevalence of CI are difficult to estimated from published data [5, 6, 10, 11], as many imaging studies, especially those with patient cohorts, exclusively recruited subjects without CIs and willing to undergo MRI. Population-based studies, in which subjects are allowed to participate independent from their participation in MRI, and studies that established MRI in one of several follow-up examinations report proportions of “scannable” participants between 37 and 93 % [9, 12–22]. However, only a few of these studies report specific reasons why the remaining subjects were not scanned. Further difficulties arise from the fact that the definition of contraindications is not consistent, as different studies apply different exclusion criteria depending on scanner type (magnetic field strength, coil selection), study-specific characteristics of the participants (e.g. obesity), individual directives of the local safety advisors and the underlying research question. Furthermore, the algorithm used to calculate the number of refusals and contraindications varies as several study protocols ask for potential CI only after participants agreed to MRI (i.e. an inaccessible number of CIs remain among the participants refusing MRI). Furthermore, self-reported claustrophobia is classified as CI in some cases and as refusal in others. Another rarely studied aspect is the influence of age structure and gender ratio on the prevalence of CIs and refusals. Occasionally, scannable participants are reported to be younger and, in terms of cardiovascular risk factors, healthier than non-scannable subjects [14].

The prevalence of IFs in cerebral MRI has been published in several studies and a meta-analysis [23]. However, most of them focus on reporting anatomic-biological pathologies, whereas study design and planning require information on clinical relevance and implied need for action (as shown by [24]). Meanwhile, the handling of IFs is a common topic for interdisciplinary discussions whereas standard procedures and recommendations are largely lacking [25–28].

We here report the approach to MR imaging in the longitudinal BiDirect study along with results on participation rates and their potential explanatory variables like age, gender and medical conditions. In particular, we report the proportions of contraindications and refusals at baseline and the first follow-up. We also describe the management and disclosure of incidental findings to facilitate planning of future studies.

Methods

Study design and study population

The interdisciplinary BiDirect study is a long-term study designed to evaluate the bidirectional relationship between major depression and (subclinical) arteriosclerosis. The examination program includes, beside others, vascular diagnostics, an interview on risk factors and MR imaging of the brain. The ethics committee of the University of Münster and the Westphalian Chamber of Physicians (Münster, Germany) approved the project and written informed consent was obtained from all participants.

Overall, 2258 participants within the age range of 35–65 years were recruited in three parallel cohorts. Cohort 1 consists of 999 patients who suffered from a clinically manifest depression and were hospitalised in one of several psychiatric hospitals in and around the city of Münster. Cohort 2 consists of 347 patients who suffered from manifest cardiovascular disease (CVD), mainly acute myocardial infarction, and were hospitalised in one of several cardiology departments or rehabilitation clinics in the region of Münster. Cohort 3 (control group) consists of 912 community-dwelling adults who had been sampled randomly from the population register of the city of Münster. Basic demographic data of participants are included in Table 3.

The baseline (BL) examinations took place between July 2010 and June 2013. The first follow-up (FU) examination started in July 2013 and was completed in December 2015.

An in-depth description of the rationale and design of the BiDirect study is provided by Teismann et al. [8].

MR imaging

A detailed description of the examination procedure along with all technical information on the protocol for cerebral MRI in the BiDirect study is provided in the [Supplementary material](#).

In summary, a multilevel procedure involving the study centre as well as the Institute of Clinical Radiology was implemented for the assessment of MR contraindications. Potential CIs are (re-)determined at every appointment. On several occasions, study participants can decide on their consent for MRI independent from participation in other study modules and separately for each examination wave.

For data interpretation, CIs were categorised according to Table 1. Self-reported claustrophobia is not classified as CI, but understood as (voluntary) refusal.

All acquired images are promptly examined with regard to incidental findings by the radiologist in charge and validated by an experienced specialist for neuroradiology. Similar to the approach of the SHIP study [24], findings were categorised according to clinical relevance (Table 2).

If requiring urgent further diagnostics or treatment (category III), findings are immediately communicated to the study centre and disclosed to the participant. In all other cases, a written report is sent to the investigators. In the case of findings that require further but not urgent medical evaluation (category II), an interdisciplinary panel of experts decides—on the basis of previously compiled lists, but finally on a case-by-case basis—if and how (phone call and/or postal mail) the finding will be disclosed to the subject and which further diagnostic steps will be recommended.

In agreement with the local ethics committee, every participant has the possibility to decline the disclosure of IFs. However, this option does not hold for pathological findings that could be a threat to others.

Statistical analysis

Prevalence of contraindications as well as refusals and their associations with age, gender and cohort at baseline and in the first follow-up are reported using descriptive statistics and logistic regression analyses, respectively. An extended logistic regression analysis that additionally includes the covariates

education, anxiety and cognitive functioning is presented in the [Supplementary material](#). As the number of scannable participants was very small and the differences in the distributions of CIs and refusals in cohorts 1 and 3 were obvious, cohort 2 (CVD patients) was not included in the cohort comparisons.

Contraindications were given more weight than refusal, i.e. only participants without CIs can refuse MRI. In the presence of several CIs, the CI from the highest category was counted.

Results

Overall, 2258 participants underwent the BiDirect baseline examination (Table 3). As a result of logistic reasons (schedule difficulties, maintenance or repair work on the scanner), 79 (3.5 %) of them could not be offered MRI and an additional three (0.1 %) subjects terminated their examination in the study centre prior to MRI because of MRI-independent reasons. The remaining 2176 participants constitute the evaluable study population.

Contraindications

The prevalence of CI in the study population is 20 % (430 cases). In the control group (cohort 3), 9 % of the subjects have at least one CI. This proportion is independent from age, but men have a 5.7-times higher probability of having CI than women. In patients with CVD (cohort 2), 76 % of the subjects were excluded from MRI, independent from age and gender. In patients with depression (cohort 1), 9 % of the subjects show at least one CI. The proportion is independent from gender, but increases by around 5 % per year of age, from 7 % (≤ 45 years) to 15 % (> 55 years). Compared to the control group and after correction for age and gender, patients suffering from depression do not have an increased probability of having a CI.

CIs of category A caused 4 % (17 cases) of exclusions. The proportion of affected participants is roughly the same across cohorts. CIs of category B caused 61 % (262 cases) of

Table 1 Categorisation of contraindications for MR imaging

Cat. A	Active implants (active implanted medical devices (AIMDs), e.g. cardiac pacemakers, implantable cardioverter defibrillators, implantable insulin pumps, cochlea implants)
Cat. B	Contraindications in consequence of cardiosurgical procedure or coronary interventions (coronary artery stents, potentially ferromagnetic vascular clips or thorax cerclage following bypass surgery); handled as absolute contraindication during the first year vafter the intervention, afterwards individual decision of MR safety managers
Cat. C	Metal foreign bodies around head or neck (e.g. metallic splinters in the eye, magnetically adhering dentures, aneurysm clips); formerly or currently metal-working participants with a history or risk of potentially ferromagnetic metallic splinters in the eye need a certificate of ophthalmologic clearance in order to be approved for MR imaging
Cat. D	Pregnancy or other contraindications after case-by-case decision (e.g. recently implanted ferromagnetic implants in the upper body, implants without sufficient information on material composition, tattoos with suspected ferrous pigments in the upper body, severe overweight, known seizure disorder)

Table 2 Categorisation of neuroradiological findings according to clinical relevance and mode of handling

Cat. I	Normal findings, anatomical variations within the normal range (e.g. cavum septi pellucidi), known pathologies or (common) findings without prognostic relevance (e.g. developmental venous anomalies, minor atrophy in elderly subjects)
Cat. II	Findings that require further radiological or medical evaluation
a	Findings where radiological assessment is equivocal and where further (MR) imaging is recommended, either with additional sequences or contrast agents or over the course of time (e.g. falx calcification with differential diagnosis meningioma, suspected inflammatory or neoplastic lesions)
b	Findings where radiological assessment is relatively straightforward on the basis of the present images and that require further medical examinations (e.g. old brain infarcts, space-occupying cysts, suspected normal pressure hydrocephalus, white matter lesions of suspected vascular origin ^a)
Cat. III	Findings that require immediate medical referral (e.g. suspected acute ischemic or haemorrhagic stroke, space-occupying neoplasms)

^a White matter hyperintensities were categorised as category II finding (i.e. potential vascular lesions requiring further medical evaluation) if the radiologists and the members of the expert panel had decided—on the basis of their clinical expertise and with regard to visual appearance of the lesions, the MRI image as a whole, and basic information on the participant—that WMHs, first, appeared typically vascular and, second, were extensive (usually diffuse confluent) or unusual regarding the participant's age

exclusions. The proportion of affected participants was 91 % in patients with CVD (mainly as a result of recently implanted cardiac stents) and 15 % in patients with depression and the control group, respectively. CIs of category C caused 25 % (109 cases) of exclusions. They constitute the main reason for MRI exclusions in patients with depression (59 % affected) and the control group (63 % affected). In patients with CVD,

the proportion of affected participants was 3 %. The remaining 42 (10 %) participants were excluded because of CIs of category D.

As a result of the questionnaire on CIs, 90 % (387 cases, including all CIs of categories A and B) of them could already be identified in the study centre. The remaining 43 participants were excluded from MRI by the radiologist in charge.

Table 3 Baseline characteristics of the study population ^a

	Cohort 1 (depression)	Cohort 2 (CVD)	Cohort 3 (control)	All
BiDirect baseline participants				
<i>N</i>	999	347	912	2258
Female	593	49	464	1106
Age (years), mean ± SD	49.79 ± 7.29	55.09 ± 5.87	52.83 ± 8.20	51.83 ± 7.92
Subjects excluded from analysis				
No MRI due to logistic reasons	10	2	67	79
No MRI due to premature termination of study examinations	1	0	2	3
Subjects without MRI				
Due to MR contraindication	93	262	75	430
Due to refusal of MR scan	159	31	96	286
Subjects with incomplete MRI	4	0	3	7
Subjects with completed MR examination				
<i>N</i>	732	52	669	1453
Female	434	11	349	794
Age (years), mean ± SD	49.35 ± 7.29	56.78 ± 5.87	52.67 ± 8.20	51.14 ± 7.92
Additional rs-fMRI	727	51	665	1443
Additional fMRI	632	43	538	1213

SD standard deviation, CVD cardiovascular disease, *N* number of participants, MRI magnetic resonance imaging, fMRI functional magnetic resonance imaging, rs-fMRI resting-state functional magnetic resonance imaging

^a Data are presented as frequencies unless specified otherwise

Refusal

Despite having no medical CI, 286 (16 %) out of 1746 permitted participants refrained from undergoing MRI. In 242 cases (85 %), the participants disagreed in their informed consents, whereas 44 participants changed their mind either in the course of the pre-examination discussion or during the positioning procedure in the scanner. Reasons for refusal were not consistently recorded, but claustrophobic fears and own concerns about medical conditions, which are not a CI to MRI, were repeatedly mentioned.

In the control group, the proportion of refusal is 13 %. While stable with increasing age, the probability of refusal is twice as high in women as in men. In patients with CVD, the proportion of refusal is 37 %, without association with age and gender. In patients with depression, the proportion of refusal is 18 %. The probability of refusal is 1.7 times as high in women compared to men and increases by about 3 % per year of age from 13 % (≤ 45 years) to 20 % (> 55 years). Compared to the control group and after correction for age and gender, the probability of refusing the MRI is increased in patients with depression by a factor of 1.6. Complete results of the statistical analysis are presented in Table 4. A visualisation of the thus far presented results is included in the [Supplementary material](#).

Prematurely terminated MRI examinations

Seven (0.5 %) out of 1460 initiated MRI examinations had to be terminated prematurely. The reasons were request of the participant (two cases), instruction of the radiologist as a result of alarming artefacts shown in the localizer (one case) or

software problems (four cases; diffusion-weighted images could not be acquired). As radiological diagnosis was still possible for the last four participants, a total of 1457 structural MRI data sets remain for the evaluation of incidental findings.

Completed MRI examinations at baseline

Overall, 1453 complete structural MRI data sets were acquired, which corresponds to 67 % of all study participants. The percentage of scannable participants is 79 % (669 data sets) in the control group, 74 % (732 data sets) in patients with depression and 15 % (52 data sets) in patients with CVD. Compared to the whole study population, the distributions of age and gender remain unchanged in the group of scannable participants. In addition, 1213 functional MRI (fMRI) data sets (with emotion processing task) and 1443 resting-state fMRI data sets have been acquired at baseline.

Disclosure of incidental findings

Three of 1457 participants declined the disclosure of findings. From the remaining 1454 participants, 1195 (82 %) received notices that their MRI data do not hold any evidence of a (novel) pathological cerebral finding or about findings without prognostic relevance (category I). In 254 (17 %) cases, the study centre recommended further radiological or medical evaluation. More precisely, in 153 cases subjects were recommended to visit their treating physician for evaluation of their cardiovascular risk profile because of suspected microangiopathy (extensive or, concerning the subject's age, unusual white matter hyperintensities, category IIb). Another 43 participants were

Table 4 Odds ratios with 95 % confidence intervals (OR) for the association of age, gender and depression with the probability of MR contraindication and proportion of refusal ^a

	Contraindication		Refusal	
	<i>N</i>	OR	<i>N</i>	OR
Cohort 1 (depression)	988		895	
Age (years)		1.05 [1.02; 1.08]		1.03 [1.00; 1.05]
Female		0.39 [0.25; 0.60]		1.67 [1.16; 2.45]
Cohort 2 (CVD)	345		83	
Age (years)		0.97 [0.93; 1.01]		0.95 [0.88; 1.03]
Female		0.54 [0.29; 1.06]		0.89 [0.28; 2.68]
Cohort 3 (control)	843		768	
Age (years)		1.01 [0.98; 1.04]		1.02 [0.99; 1.05]
Female		0.18 [0.09; 0.32]		2.01 [1.28; 3.21]
Cohorts 1 + 3	1831		1663	
Age (years)		1.03 [1.01; 1.05]		1.02 [1.00; 1.04]
Female		0.29 [0.20; 0.41]		1.80 [1.35; 2.42]
Depression		1.29 [0.93; 1.81]		1.57 [1.19; 2.09]

N number of participants, *CVD* cardiovascular disease

^a All categorical variables are coded as 1 = yes/0 = no, unless specified otherwise. Odds ratios that are significantly different from 1 at the 5 % level are indicated in bold

informed (by postal mail or by phone) about other category IIb findings and 55 participants received recommendations about “uncertain” findings (category IIa) to be re-examined or monitored. Two participants were advised to undergo an ophthalmological examination prior to the next MRI examination because of noticeable image artefacts and one report held the recommendation to have an extracranial pathology checked by a dermatologist. Finally, in 5 (0.3 %) cases the expert panel decided to disclose the findings (i.e. space-occupying neoplasms in two cases, suspected acute ischemic stroke in two cases and suspected subacute micro-haemorrhage in one case) on the same day and informed the participants either in a face-to-face talk or by phone (category III).

Follow-up examinations

A total of 1089 subjects who completed MRI at baseline participated in the first BiDirect follow-up examination. MRI examination could not be offered to 18 participants because of logistic reasons. In 35 (3 %) of the remaining cases the participants were excluded as a result of incident CI, and an additional 75 (7 %) participants disagreed with repeated MRI examination. Furthermore, 327 participants who were excluded as a result of CIs at baseline did participate. Beside 221 participants who still have CIs, 101 (31 %) participants were now approved for MRI examination. However, 17 (17 %) of them refused. MRI could not be offered to the remaining five participants because of logistic reasons. Finally, 163 participants who refused the MRI examination at baseline participated. As a result of incident CI, 27 (17 %) participants were excluded from MRI. Nevertheless, 40 (30 %) of the remaining 135 participants now agreed to undergo MRI. Detailed information is presented in Table 5.

Table 5 Frequencies of contraindications (CI) and refusals at follow-up (FU) examination stratified according to baseline (BL) status

	MRI at BL	CI at BL	Refusal at BL
<i>N</i>	1453	430	286
With FU appointment	1089	327	163
Subjects without MRI			
Due to logistic reasons	18	5	1
Due to CI	35	221	27
Due to refusal	75	17	95
Subjects with incomplete MRI	8	5	1
Subjects with complete MRI	953	79	39

MRI magnetic resonance imaging, *BL* baseline (examination), *FU* follow-up (examination), *CI* contraindication, *N* number of participants

Discussion

During the BiDirect baseline examinations, completed structural MRI data sets were obtained from 67 % of the study population. In the control group, the percentage of scannable participants was 79 %. About 9 % of all subjects had to be excluded from MRI because of contraindications with men being affected almost six times as often as women. The proportion of refusal was about 12 % and the probability of refusal was twice as high in women as in men. In the control group, neither the prevalence of CI nor the proportion of refusal was associated with age. The percentage of scannable participants in the patient cohorts was lower than in the control group. In patients with depression, 74 % of participants underwent MRI. While the prevalence of CI was as high as in the control group, the proportion of refusal was increased by about 60 %. Contrary to the control group, the considered percentages were clearly age-dependent. In patients with CVD, only 15 % of participants underwent MRI mainly as a result of the (anticipated) high number of recently implanted stents. Furthermore, the proportion of refusal was twice as high as in the other cohorts.

Available data suggests that age, gender and depression constitute the main explanatory factors for the willingness to participate in the MRI examination. Regarding other potential factors, the analyses revealed no independent association for education or anxiety. However, for patients with depression (cohort 1), a poorer performance in cognitive tests, which is most likely an indicator for disease severity, is associated with an increased proportion of refusal.

As a consequence of individual clarification of potential contraindications with treating physicians as well as MR safety managers, 90 % of all CIs and 85 % of all refusals were already recorded in the study centre. Therefore, available measurement periods could be optimally used and unnecessary expenses could be saved. Experiences of BiDirect indicate that almost two-thirds of all CIs result from (potential) metal foreign bodies around the head or neck of the participant, including a substantial number of participants who merely reported that they were working or had worked with metal. For this reason, recommending or offering an ophthalmological examination to check for metal splinters in the eye could potentially reduce the prevalence of CI. Regarding patients with CVD it is worth noting that latest statements and recommendations of cardiologic and radiologic specialist societies point towards a safe application of MRI in patients with newer passive cardiac implants under certain conditions and limitations. For example, on the basis of current knowledge and provided that the exact model of the implant is identified, many patients with cardiovascular stents can be scanned without safety concerns as early as 6 weeks after implantation [29]. Hence, experiences from clinical imaging recurrently hold opportunities to reduce CIs for scientific imaging studies.

Since neither participants nor study employees can generally influence the presence of CIs, the proportions of refusal were only evaluated in those participants who were approved for MR examination. Nevertheless, individual subjects could have known about their CI and “conveniently” refused to undergo MRI without providing further information. This assumption is supported by the fact that the incidence of CI in the group of formerly refusing patients was considerably higher than in the group of formerly examined participants (17 % vs. 3 %). Moreover, this fact also provides a reasonable explanation for the remarkably high proportion of refusal in patients with CVD (cohort 2).

Less than 1 % of all neuroradiological findings gave cause for an immediate medical referral. However, 17 % of all scanned participants were recommended to see a physician in order to evaluate their risk profile, to be re-examined or to be monitored. These 17 % are split into participants who had extensive white matter hyperintensities (WMH) consistent with cerebral microangiopathy (11 %) and participants who showed other, mainly vascular or tumorous lesions (6 %). These frequencies are in line with previously reported prevalences of (non-WMH) incidental brain findings and WMHs [23, 30], whereby the latter strongly depends on age and cohort characteristics (e.g. vascular risk profile). While IF frequencies are comparable across most population-based studies, their handling and reporting vary. The expert panel of BiDirect agreed on the disclosure of extensive WMHs accompanied by a recommendation for screening of cardiovascular risk factors owing to the considerably increased risk of stroke and dementia in patients with WMH [31]. It is further notable that the majority of (non-WMH) brain findings are of uncertain nature and relevance, which has also been pointed out in other population studies [24]. From the participants’ point of view, the potential medical benefit from early diagnosis competes with the (potentially unnecessary) psychosocial burden. Leaving this essential consideration largely unattended is a limitation of the present study. However, in cooperation with the SHIP study team, who systematically investigated the psychosocial consequences of disclosed IFs [32], all BiDirect participants have been interviewed during FU examination about the psychosocial as well as medical consequences of their disclosed findings at BL.

At follow-up examinations (on average 2.5 years after baseline), 3 % of participants report incident, i.e. new, contraindications and 7 % refused repeated MRI. In contrast, from about one-quarter of participants who were excluded from or refused MRI at BL, complete MR data sets could be acquired during FU examination. Thus, in longitudinal studies with multiple examination waves, the re-evaluation of CIs and refusal is rewarding.

In summary, the prevalence of contraindications for MRI and the proportion of refusal clearly depend on age, gender and medical conditions of the participants. Therefore, cohort-

specific characteristics should be considered for sample size calculations and the current status of each participant should be individually clarified at each re-invitation.

Extensive white matter hyperintensities account for the largest number of IFs in brain MRI, whereas the majority of other findings are of uncertain nature or clinical relevance. To face this issue, the establishment of an expert panel is beneficial. Also study participants should be conscientiously informed about the uncertainty of IFs revealed by the study.

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