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Supplemental imaging modalities for breast cancer screening in women with dense breasts: A systematic review with economic considerations

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A B S T R A C T

Background: Underdiagnosis of breast cancer is a concern for women with dense breasts. This systematic review and meta-analysis evaluates the performance and cost-effectiveness of supplementary imaging modalities plus standard mammography, versus mammography alone, for detecting breast cancer in women with dense breasts.

Methods: We searched MEDLINE, Embase, Scopus, Cochrane Database, Web of Science, and CENTRAL for English-language studies published January 2014 to November 2024. Eligible studies compared the performance of a supplementary imaging modality with standard mammography in terms of cancer detection rate (CDR) in women with dense breasts undergoing screening. Risk of bias was assessed using QUADAS-2/QUADAS-C. Screening, data extraction, and quality assessment was conducted by one reviewer and checked by a second reviewer. PROSPERO: CRD42024550250.

Results: Out of 1740 search results, 36 studies met the inclusion criteria. Versus mammography alone, magnetic resonance imaging (MRI) identified 18·92 (95 % CI 15·41-22·43) additional cancers per 1000 screenings while digital breast tomosynthesis (DBT), automated breast ultrasound (ABUS), and handheld ultrasound (HHUS) detected 1·69 (95 % CI 0·81-2·58), 2·3 (95 % CI 1·28-3·33), and 2·57 (95 % CI 0·99-4·14) additional cancers, respectively. One study of contrast-enhanced mammography (CEM) reported a CDR comparable to MRI. Economic modelling studies revealed heterogeneous results, with MRI showing potential under specific model assumptions.

Concluding statement: Standard mammography often fails to detect cancers in women with dense breasts. Supplementary MRI provides better detection than DBT, ABUS, and HHUS. CEM seems comparable to MRI, based on limited evidence. These findings should be considered in future screening policy reviews for women with dense breasts.

1. Introduction

Breast cancer caused 670,000 deaths globally in 2022 and was the most common cancer in women in 157 countries out of 185 in that year, according to the World Health Organisation (WHO) [1]. In the UK, there were 56,822 new diagnoses annually between 2017 and 2019 [2]. The WHO Global Breast Cancer Initiative (GBCI) aims to achieve a 2.5 % annual reduction in breast cancer mortality by 2040 based on three pillars: health promotion for early detection; timely diagnosis; and comprehensive breast cancer management [1].

Whilst breast cancer screening remains one of the most effective strategies for reducing breast cancer mortality in average-risk women [3], underdiagnosis continues to be a critical concern for individuals with dense breasts, classified as categories C and D under the American College of Radiology (ACR) BI-RADS system [4]. Breast density describes the amount of fibroglandular tissue in the breast relative to the amount of fatty tissue. Because most cancers absorb X-rays to a similar extent as fibroglandular tissue, they appear as white areas on a mammogram. Consequently, dense (white) tissue can obscure or'mask' cancers, making them more difficult to detect on mammography [3].

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Women classified as BI-RADS categories C and D, encompassing nearly half of those screened [5], have an increased risk of developing breast cancer and an increased risk of missed diagnoses due to the reduced sensitivity of standard mammography in dense breasts [6]. Despite these challenges, recent advances in breast imaging technology offer promising solutions. A previous systematic review, which included studies up to March 2020, found that magnetic resonance imaging (MRI) was superior to other supplemental modalities for the detection of breast cancer in individuals with dense breasts and intermediate or average risk of breast cancer [7]. The European Society of Breast Imaging (EUSOBI) recommend that women with extremely dense breasts be offered supplemental MRI [8], but suggest that ultrasound could be performed if MRI is not available, with the caveat that the added value of supplemental ultrasound is limited. The recently concluded UK BRAID study investigated the effectiveness of an abbreviated MRI (Ab-MRI) protocol, contrast-enhanced mammography (CEM), and automated breast ultrasound (ABUS) in enhancing cancer detection in individuals with dense breasts. BRAID found that Ab-MRI and CEM identified three times as many invasive cancers as ABUS [9].

This review aimed to determine the effect of an additional imaging modality to supplement standard screening mammography, compared with mammography alone, for the detection of breast cancer in women with dense breasts. An accompanying economic review sought to assess the cost-effectiveness of supplemental imaging modalities for breast cancer screening in women with dense breasts.

2. Methods

2.1. Search strategy and selection criteria

This systematic review and meta-analysis followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [10] and adhered to the Preferred Reporting for Systematic Reviews (PRISMA) statement [11]. It was prospectively registered (PROSPERO registration CRD42024550250) [12] and supported by an Advisory Group, comprising content experts, methodological specialists, and patient partners. The research question was framed using the PICOS criteria: the **Population** of interest was women aged 40–70 undergoing screening, stratified by breast density categories; the **Intervention** comprised supplemental imaging modalities for women with dense breasts including MRI (full/abbreviated protocol), CEM, ultrasound (hand-held or automated), and digital breast tomosynthesis (DBT); the **Comparator** was standard mammography alone; the **Outcomes** of interest included cancer detection rate (CDR), interval cancer rate, recall rate, positive predictive values (PPV), false positive rate, sensitivity, specificity, cancer stage, and time needed for the additional imaging modality to be performed; and the relevant **Setting** was breast cancer population screening. We focused on **Studies** published in English in the last 10 years. Standard mammography, used as the comparator intervention, was defined as digital 2D mammography, consistent with current practice in the UK. The four categories of breast density described according to the ACR BI-RADS atlas are [4].

a. The breasts are almost entirely fatty

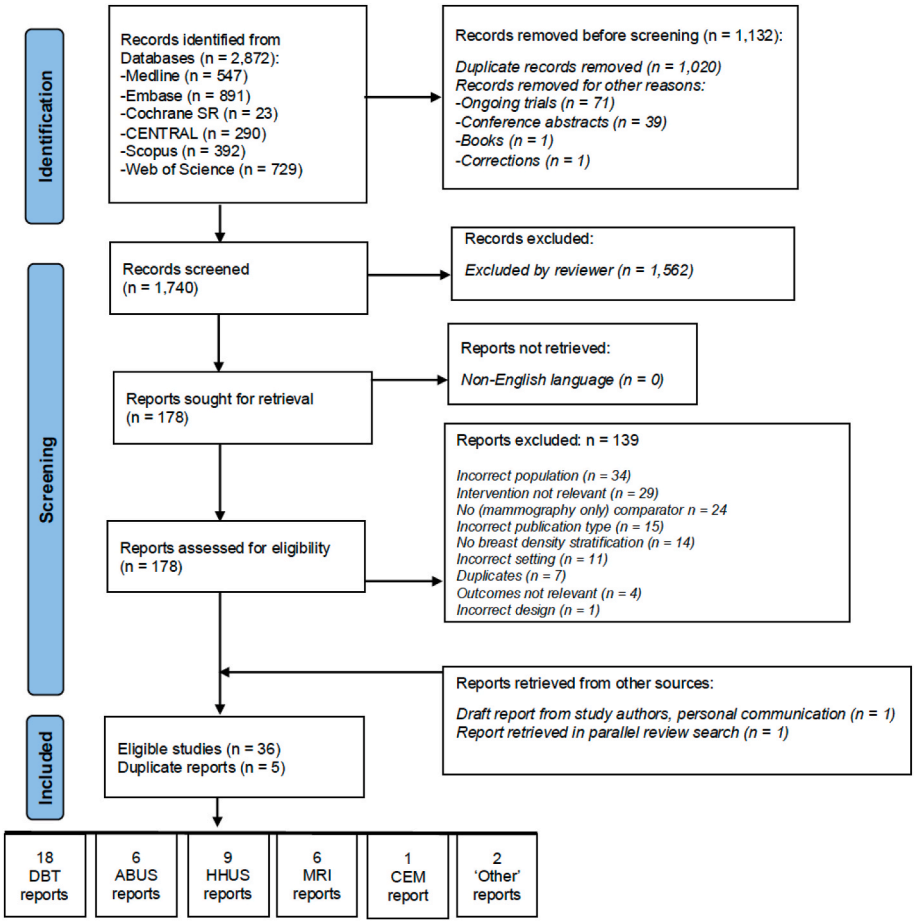

Fig. 1. Study selection DBT, digital breast tomosynthesis; ABUS, automated breast ultrasound; HHUS, hand-held ultrasound; MRI, magnetic resonance imaging; CEM, contrast enhanced mammography. As some studies reported on more than one supplementary imaging modality, the number of reports providing information in each imaging modality (42) exceeds the number of included studies (36).

b. There are scattered areas of fibroglandular density
c. The breasts are heterogeneously dense, which may obscure small masses
d. The breasts are extremely dense, which lowers the sensitivity of mammography

An Information Specialist (PM) conducted searches across major databases (Fig. 1) focusing on full-text studies published 2014–2024 (Appendix A), with most recent searches in November 2024. Reference lists of relevant articles were screened for additional studies. Full texts of potentially relevant articles were evaluated by one reviewer (SD), with 20 % assessed by a second reviewer (CR). Disagreements were resolved through discussion or consultation with other authors (MB, ST, MC). Studies evaluating the role of additional imaging modalities in individuals with negative mammography results were deemed suitable for inclusion, and data specific to the supplemental imaging modality were extracted. While the primary population of interest was women aged 40–70 years, we did not exclude participants from other age groups if they were undergoing population-based screening.

2.2. Data analysis

Data recorded from included studies encompassed study characteristics (first author, year, recruitment dates, location, centres, language, screening setting, objectives, inclusion and exclusion criteria), participant characteristics, number and experience of health professionals measuring breast density, screening frequency, and details of imaging modalities. Data extraction was performed by one reviewer (SD) and verified by a second (EMcC), with the AI Assistant feature in Adobe Acrobat used for cross-checking. Disagreements were resolved through discussion. All data were documented using a bespoke Microsoft Excel® form. The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool assessed risk of bias in individual studies across four domains: patient selection, index test, reference standard, and flow and timing [13]. For comparative accuracy studies, the QUADAS-C version was used [14]. Assessments were performed by one reviewer (SD) and verified by a second reviewer (GV), using a bias guidance table developed in consultation with our Advisory Group (Appendix B). Multiple publications on the same study were combined, and potential duplicates were examined, with authors contacted as needed. Preliminary reports of subsequently published data were excluded from the final set. Findings were summarised narratively and, where appropriate, through meta-analyses. Results for each imaging modality were presented separately. For relevant outcome measures (e.g., CDR, recall rate) pooled effect estimates with corresponding 95 % CIs were calculated using a random-effects model. Meta-analysis results are presented in tabular form and illustrated graphically using forest plots [15]. The effect size shown for each study is the difference in the respective outcome between the supplemental modality and mammography-only. In Table 2 the outcome measure in the mammography group is presented with the difference between the specific modality and mammography shown in the next row of the table. To explore the influence of small study sizes, the study's Advisory Group recommended sensitivity analysis excluding studies with fewer than 500 participants. Heterogeneity between studies was quantified using the I^2 statistic and examining forest plots, with thresholds indicating low (<30 %), moderate (30–60 %), or substantial (>60 %) heterogeneity [16]. Analyses were performed using Stata 18 [17].

2.3. Patient and public involvement (PPI), and language and inclusivity statement

PPI partners with lived experience of mammography and breast cancer contributed to our Advisory Group alongside content and methodological experts. They actively participated in all project meetings and provided input across all review stages. While the UK breast screening programme primarily targets women, this review intentionally uses both gender-specific and gender-neutral language to acknowledge all individuals who access breast screening services.

Role of funding source

This review was funded by the National Institute for Health and Care Research (NIHR) Evidence Synthesis Programme (project number NIHR164221) and commissioned by the United Kingdom National Screening Committee (UK NSC). The UK NSC provides screening recommendations to the UK government, based on a range of criteria, including a consistent approach to the identification and synthesis of relevant literature. The UK NSC and NIHR have recently agreed on a formal collaboration to ensure the quality of evidence reports. The NIHR Evidence Synthesis Programme had no role in the collection, analysis, or interpretation of the data; in the writing of the report; or in the decision to submit the article for publication. The UK NSC, as commissioners of the work, participated in the Advisory Group and provided expert input on study design, data interpretation, and the current screening pathway. However, they had no role in writing the manuscript, formulating the conclusions, or deciding to submit it for publication.

2.4. Economic evaluation

A review of economic evaluations assessing the costs and consequences of supplemental imaging modalities for breast cancer screening in women with dense breasts was conducted in parallel and is summarised briefly in this manuscript. The search strategy and PRISMA flowchart for the economic review are in Appendices C and D.

3. Results

A total of 1740 citations were identified from the literature searches, with 178 reports selected for full-text screening. Forty-one relevant studies were identified, including two articles from additional sources (Fig. 1), one of which was accessed in its prepublication version and subsequently published [9]. After removing five duplicates, 36 studies were included, ten of which were published between 2023 and 2025 [9,18–26]. Publications excluded after review of full text are listed in Appendix E. The studies were geographically distributed: 16 in Europe [9,22,24,26–38], 10 in North America [39–48], and 10 in Asia [18–21,23,25,49–52]. Digital breast tomosynthesis (DBT) was the most frequently assessed modality (18 studies) [22,24,27,33,34,36–45,47,48,50], followed by handheld ultrasound (HHUS, nine studies) [19–21,23,25,28,37,51,52], ABUS (six studies) [9,18,20,29,32,46], MRI (six studies) [9,26,30,31,35,49], whole breast sonography (WBS, one study) [45], and CEM (one study) [9]. For all MRI studies, only participants with a negative mammography received MRI. Full-protocol MRI was used in five studies [26,30,31,35,49], while an Ab-MRI was adopted in two studies [9,49] (one study compared both protocols) [49]. Table 1 illustrates the characteristics of the included studies. Reporting of equality, diversity and inclusion (EDI) characteristics was generally poor.

Most studies had low risk of bias in the domain of patient selection; however, five studies (14 %) were rated as high risk due to opportunistic selection [19,23,41,48,50] and unclear reporting [23]. Applicability concerns were identified in 15 studies (41 %), mainly due to age profiles that did not align well with the UK screening programme [18,19,36,44,46,49,51,52], or inclusion of women with extremely dense breasts only [30,35]. A further study was flagged for applicability concerns as approximately 65 % of MRI participants had a negative ultrasound as well as a negative mammography [31], and an unspecified number of individuals had negative ultrasounds and were ineligible for the MRI study. Therefore, the comparator arm had an advantage over the mammography-only arm, likely leading to an underestimation of MRI's cancer detection performance [31]. Seventeen studies (47.2 %) were at

Table 1
Reported characteristics of included studies for each supplementary imaging modality plus mammography in women with dense breasts.

Study name Author, year (country)	Supplementary screening modality/ comparator imaging (interval between tests)	Design (number of centres)	Study years	Number with dense breasts in study arm/ number with dense breasts in DM only arm [a]	Brief population description Age[b]	Screening programme interval	Reference standard
DBT							
CBTST Pulido-Carmona, 2024 [22] **(Spain)**[c]	DBT/DM (Interval: simultaneous)	Retrospective study (1)	2015 Jan to 2016 Dec	4207/8950	People 50-69y resident in Cordoba participating in breast cancer screening Age NR	Biennial	Linkage with multiple registries and database of centre's Breast Unit
MBTST Olinder, 2023 [24] **(Sweden)**	DBT/DM (Interval: simultaneous -acquired at one screening occasion)	Prospective screening trial (1)	2010 Jan to 2015 Feb	6645/6, 645 (participants underwent both imaging modalities)	Random sample of people 40-74y selected from screening registry in Malmö, Sweden Age NR (reported for highest density quintiles only)	NR	NR
RETomo Pattacini, 2022 [34] **(Italy)**	DBT/DM (Interval: simultaneous)	RCT (3)	2014 Mar to 2017 Aug	5970/5978	People aged 45–69y attending screening in one of three clinics Age NR	45–49 y annual 50–74 y biennial	All recruited people followed up in screening programme and Cancer Registry Evaluation of surgical specimen considered final diagnosis of lesion
Durand, 2021 [42] **(USA)**	DBT/DM (Interval: NR)	Retrospective study (10)	DBT start dates between 2011 Apr and 2012 May to 2013 Jun DM start dates NR	86,571/95,914	Screening examinations from 10 academic and community practices Age: 40-49y: 113,950 (29.9 %) 50-69y: 209,753 (55.1 %) ≥70y: 45,019 (11.8 %)	Annual	Linkage to site and state cancer registries
Pang, 2021 [47] **(Canada)**	DBT/DM (Interval: simultaneous; combined DBT and DM)	Observational (2)	2015 to 2018	58,281/67,489	People ≥40y who underwent screening at two large volume multisite radiology groups in Alberta, Canada Age NR	Biennial	Linkage to Alberta Cancer Registry
Ban, 2021 [50] **(Japan)**	DBT/DM (Interval: NR)	Prospective trial (1)	2017 May to 2019 Mar	1739/4226	People attending population-based screening in Japan who also had opportunistic DBT screening (workplace/private) and were >30y Age: NR	Biennial	NR
Oslo Tomosynthesis Screening Trial Osteras, 2019 [27] **(Norway)**	DBT/DM (Interval: simultaneous [combined DBT and DM])	Prospective clinical trial (1)	2010 Nov to 2012 Dec	8466/8466 (participants underwent both imaging modalities)	People aged 50-69y attending population-based screening program, BreastScreen Norway Age: 50–54y: 3158 55–59y: 2390 60–64y: 1574 65–69y: 1624	Biennial	2 years of follow-up to assess interval cancers
Stepanek, 2019 [48] **(USA)**	DBT/DM (Interval: simultaneous; combined DBT and DM)	Retrospective review (1)	DM: 2010 Sep to 2011 Aug DBT/DM: 2014 Jan to 2015 Jun	4389/4895	Screening programme with DM; DBT made available at an additional charge Age NR	Annual	Category 3 lesions followed for minimum 2 y or cross-referenced with the state tumour registry Negative findings BIRADS 1/2 resumed annual screenings
MBTST Johnson, 2019 [38] **(Sweden)**	DBT/DM (Interval: simultaneous -one screening occasion)	Prospective, population-based screening trial (NR)	2010 Jan to 2015 Feb	6202/6202 (participants underwent both imaging modalities)	Random sample of people from screening registry in the city of Malmö, Sweden Age NR	NR	Pathologic assessment of surgical specimens Linkage with Cancer Registry

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Table 1 (*continued*)

Study name Author, year (country)	Supplementary screening modality/ comparator imaging (interval between tests)	Design (number of centres)	Study years	Number with dense breasts in study arm/ number with dense breasts in DM only arm [a]	Brief population description Age[b]	Screening programme interval	Reference standard
Upadhyay, 2018 [36] **(UK)**	DBT/DM (Interval: simultaneous)	Retrospective reader study (1)	2013 Jan to 2013 Dec	423/423 (participants underwent both imaging modalities)	People aged 46–53 were recruited from the prevalent screening round of the NHS Breast Screening Programme Age NR	Triennial	Recalls: Assessment within 3 weeks (further imaging, biopsy as appropriate)
Rose, 2017 [44] **(USA)**	DBT/DM (Interval: Simultaneous -combined DBT/DM for all or part of the analysis period)	Retrospective review of screening mammography audit data (31)	2015 Jan to 2015 Dec	10,360/21,929	Community-based screening programme for people <50y Age NR	NR	Data validated by auditing patient outcomes, imaging reports, and pathology results for biopsy and surgical specimens
Freer, 2017 [41] **(USA)**	DBT/DM (Interval: simultaneous)	Retrospective study with institutional databases (NR)	2013 Oct to 2014 Dec (cohort 3 end date 2015 Dec)	521/8302	People who presented for screening MM to any screening facility of their academic medical centre Cohort 2: Under 40: 1.7 %; 40–49: 27.5 %; 50–59: 34.2 %; 60–69: 25.3 %; 70–74: 6.9 %; Over 74: 4.4 % Cohort 3: Under 40: 1.4 %; 40–49: 26.0 %; 50–59: 31.7 %; 60–69: 25.5 %; 70–74: 7.8 %; Over 74: 7.6 %	NR	NR
STORM-2 Bernardi, 2016 [33] **(Italy)**	DBT/DM (Interval: simultaneous)	Prospective population-based screening study (1)	2013 May to 2015 May	2592/2592 (participants underwent both imaging modalities)	People >49y attending population-based screening programme Age NR	Biennial	Biopsy Recalled patients: completed assessment outcome, inclusive of work-up imaging (with or without biopsy)
Starikov, 2016 [45] **(USA)**	DBT/MM (Interval: same day)	Retrospective observational case–control study (1)	2013 Jan to 2013 Dec	1875/7117	People presenting for screening mammography Age: Majority of patients >40y	Annual	List of biopsy proven screen-detected breast cancers
PROSPR Conant, 2016 [43] **(USA)**	DBT/DM (Interval NR)	Retrospective analysis of prospective cohort data (3)	2011 to 2014	21,133/44,303	People 40-74y with no known prior breast cancer Age: 40–49 years: 37,155 (26.0 %) for DM, 18,668 (33.3 %) for DBT 50–59 years: 51,096 (35.8 %) for DM, 20,839 (36.4 %) for DBT 60–74 years: 54,632 (38.2 %) for DM, 16,941 (30.3 %) for DBT	NR	Biopsy information from electronic health records and pathology databases -≥ 1 year of imaging follow-up Cancer data from local institutional tumour registries, state registries, and one statewide surveillance system
ASTOUND Tagliofico, 2016 [37] **(Italy)**	DBT/negative DM (Interval: simultaneous	Prospective multicentre study (5)	2012 Dec to 2015 Mar	3231/3231 (participants underwent both imaging modalities)	Asymptomatic people with negative MM aged 38 years or older with dense breasts Age: median (IQR) age 51 y (44–78) (of those invited to study; 64 declined to participate))	NR	Biopsy Recalled subjects: work-up imaging with or without core-needle biopsy
MacDonald, 2016 [40] **(USA)**	DBT/DM (Interval NR)	Retrospective analysis (1)	2010 Sep to 2011 Aug	3611/3489	People underdoing screening mammography at the University of Pennsylvania Mean (SD) age: DM cohort: 56.9 (11.0)	Unclear, likely annual	Biopsy Pennsylvania State Cancer Registry queried to determine interval cancer rate

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Table 1 (*continued*)

Study name Author, year (country)	Supplementary screening modality/ comparator imaging (interval between tests)	Design (number of centres)	Study years	Number with dense breasts in study arm/ number with dense breasts in DM only arm [a]	Brief population description Age[b]	Screening programme interval	Reference standard
MacDonald, 2015 [39] **(USA)**	DBT/DM (Interval NR)	Retrospective analysis of a natural outcomes experiment (1)	2010 Sept to 2013 Feb	632/405	People underdoing screening mammography at the University of Pennsylvania Mean (SD) age: DM cohort: 49.2y (10.1) DBT cohort: 48.9y (10.6)	NR	Biopsy or surgical outcomes tracked within 180 days of screening recall Min 12 months of follow-up data available for all patients in both cohorts Linkage to Pennsylvania State Cancer Registry
ABUS							
BRAID, Gilbert, 2024 [9] **(UK)**	ABUS/negative screening MM (Interval median days [IQR]: 111 [77–150])	RCT (10)	2019 Sept to 2024 Mar	2141/6306	MM-negative people attending UK population breast screening at 10 centres Median (IQR) age: 56 (52–61)	Triennial	Recall cases: further imaging and biopsy if lesion was confirmed Where doubt about lesion or not: repeat CEM or MRI/short term follow up offered
Kwon, 2023 [18] **(South Korea)**	ABUS/DM (Mean interval 4 days; range 0–90 days)	Retrospective analysis involving database search (1)	2018 Jan to 2019 Dec	2155/2155 (participants underwent both imaging modalities)	Database of consecutive asymptomatic people breast cancer screening Age profile: <50y 40 % >50y 60 %	NR	Histopathologic results from surgical excision, US-guided core biopsy or vacuum-assisted biopsy, stereotactic biopsy, or stability on follow-up imaging
Ren, 2023 [20] **(China)**	ABUS/DM (Interval NR, but people with an odd number at end of ID receive ABUS first while those with even number attend DM first – suggesting immediate)	Multicentre, population-based study (6)	2018 Feb to 2022 Aug	Total group 10,884	Asymptomatic people attending breast cancer screening in China Median (IQR) age: 51.54 (4.61)	NR	Biopsy or 1-year follow-up
Gatta, 2021 [32] **(Italy)**	ABUS/FFDM (Interval NR)	Prospective observational study (1)	2017 Jun to 2019 Feb	1165/1165	People with dense breasts attending health screening centre Age: 40-50y 68 % 50-60y 25 % 60-70y 7 %	Annual (for dense breasts)	No signs of malignancy: dense breast annual checkup Suspected malignancy: Biopsy
Wilczek, 2016 [29] **(Sweden)**	ABUS/DM (Interval: immediate)	Prospective evaluation of a breast screening programme (1)	2020 Nov to 2012 Feb	1668/1668	Asymptomatic people with dense breasts who had been invited for breast cancer service screening mammography Age: 40-49y: 59.7 % 50-59y: 26.7 % 60-69y: 13.5 %	People aged 40-49y every 18 months	Suspicious findings (DM or ABUS): recalled and subjected to mammography work–up with complementary views and HHUS [d]Code 1–2: invited to the next screening after appropriate interval [d]Code 3–5: biopsy
Somolnsight Brem, 2015 [46] **(USA)**	ABUS/DM (Interval: Immediate)	Observational, multicentre study (10)	2009 to 2019	15,318/15,318	People aged >25 years with dense breast tissue Mean (SD) age 53.3 (10)	Annual	Normal, benign, or probably benign: followed up for 12 months Developed breast symptoms during the follow-up period: clinically indicated evaluation
HHUS							
Ha, 2024 [25] **(South Korea)**	HHUS/DM (Interval NR, but some on same day)	Retrospective study (1)	2017 Jan to 2018 Dec	5707/5707	Consecutive asymptomatic people (≥40 years) with dense breasts who underwent routine screening DM and supplemental US Age: Mean (SD) age 52.4 (7.9) y	Annual	Histologic examination and 1-year follow-up data Positive cases: short-interval follow-up (6 months) and additional DM or biopsy recommended

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Table 1 (*continued*)

Study name Author, year (country)	Supplementary screening modality/ comparator imaging (interval between tests)	Design (number of centres)	Study years	Number with dense breasts in study arm/ number with dense breasts in DM only arm [a]	Brief population description Age[b]	Screening programme interval	Reference standard
Lee, 2024 [21] **(South Korea)**	US/DM (Interval: within 1 month)	Retrospective study (1)	2017 Jan to 2017 Dec	1325/1325	Patients with dense breasts who underwent both screening DM and screening US Mean 53 years, median 53 years	At least biennial	Cancer diagnosis: pathological evaluation Benign diagnoses: MM/ US follow-up documenting at least 24 months of imaging stability
J-Start Nakamura, 2024 [19] **(Japan)**	HHUS/DM (Interval NR)	Retrospective analysis of breast cancer screening data (NR)	2018 to 2021	6271/11,765	People in their 40s undergoing breast cancer screening Age: NR for people with dense breasts	NR	Positive cases referred to specialised institution
Ren, 2023 [20] **(China)**	HHUS/negative DM (Interval NR, but people with an odd number at end of ID receive ABUS first while those with even number attend DM first – suggesting immediately)	Multicentre, population-based study (6)	2018 Feb to 2022 Aug	10,884/10,884 (participants underwent both imaging modalities)	Asymptomatic people attending breast cancer screening in China with negative DM Median (IQR) age: 51.54 (4.61)	NR	Biopsy or 1-year follow-up
Rani, 2023 [23] **(India)**	US/DM (Interval: 'mammography followed by ultrasound')	Prospective, observational study (1)	NR	125/125 (participants underwent both imaging modalities)	Asymptomatic people coming for breast cancer screening Age >40y	Annual health screening - not clear if this was annual breast screening	Biopsy BIRADS 3 lesions subjected to short interval follow up and few lesions had surgical excision
J-Start Harada-Shoji, 2021 [52] **(Japan)**	HHUS/DM (Interval NR)	Secondary analysis of a randomised clinical trial (42)	2007 Jul to 2011 Mar	5797/5593	Asymptomatic people aged 40–49 years who were enrolled in J-START Mean (SD) age: 44.8 (2.8)	NR	Linkage with hospital discharge records and cancer registry databases used to identify breast cancer diagnosis information
Buchberger, 2018 [28] **(Austria)**	HHUS/DM (Interval: at same visit)	Observational data from a population-based screening program (22)	2008 Jun to 2010 May	31,918/31,918 (participants underwent both imaging modalities)	Participants identified through the Tyrolean breast cancer screening program, included all people aged 40–69 who lived in Tyrol and were covered by compulsory social insurance Age NR	Aged 40–59: annual Aged 60–69: biennial	Linking the screening dataset to all breast cancer cases collected in Cancer Registry of Tyrol
ASTOUND Tagliafico, 2016 [37] **(Italy)**	HHUS/negative DM (Interval unclear, but likely immediate)	Prospective multicentre study (5)	2012 Dec to 2015 Mar	3231/3231 (participants underwent both imaging modalities)	Asymptomatic people with negative MM aged 38 years or older with dense breasts Age: Median (IQR) 51 (44–78)	NR	Biopsy Recalled subjects: work-up imaging with or without core-needle biopsy
Chang, 2015 [51] **(South Korea)**	HHUS/negative DM (Interval unclear: 'Scheduling simultaneously performed')	Retrospective review of a database (1)	2008 Jan to 2008 Dec	990/990 (participants underwent both imaging modalities)	MM-negative people attending health screening centre 62 % of all participants <50y	NR	Most severe biopsy results within 1 year of screening and clinical follow-up at 1 year or both
MRI							
MA-DETECT Kaiser, 2024 [26] **(Germany)**	Fp-MRI/negative screening DM (Interval: not to exceed 2 months)	Prospective screening study, preliminary report (1)	2021 Jun to 2023 Jun	200/200 (participants underwent both imaging modalities)	MM-negative people attending national German breast cancer screening programme; report for first 200 people Age NR	NR	BI-RADS 3: MRI follow-up after 6 months BI-RADS 4 and 5: Biopsy (as per EUSOBI recommendations)
BRAID Gilbert, 2024 [9] **(UK)**	Ab-MRI/negative screening DM (Interval median days [IQR]: 143 [98–183])	RCT (10)	2019 Sept to 2024 Mar	2130/6306 (participants underwent both imaging modalities)	MM-negative people attending UK population breast screening at 10 centres Median (IQR) age: 56 (52–61)	Triennial	Recall cases: further imaging and biopsy if lesion was confirmed Ab-MRI group: Fp-MRI conducted when no lesion found on assessment Where doubt about lesion or not: repeat CEM

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Table 1 (*continued*)

Study name Author, year (country)	Supplementary screening modality/ comparator imaging (interval between tests)	Design (number of centres)	Study years	Number with dense breasts in study arm/ number with dense breasts in DM only arm [a]	Brief population description Age[b]	Screening programme interval	Reference standard
							or MRI/short term follow up offered
DENSE (2nd Round) Veenhuizen, 2021 [30] **(Netherlands)**	Fp-MRI/negative screening DM (Median [IQR] interval 8 [3–13] weeks)	Prospective, multicentre trial embedded within the screening programme (NR)	2011 Dec to 2016 Jan	3436/3436 (participants underwent both imaging modalities)	MM-negative people attending Dutch population based biennial screening programme for second MRI (**all extremely dense breasts**) Median (IQR) age: 54 (51–59)	Biennial	MRI screening and diagnostic work-up (biopsy and histopathological examination)
DENSE (1st Round) Bakker, 2019 [35] **(Netherlands)**	FpMRI/negative screening DM (Median [IQR] interval: 10 [I8-14] weeks)	Multicentre RCT (8)	2011 Dec to 2015 Nov	4783/4783 (participants underwent both imaging modalities)	MM-negative people attending Dutch National population-based biennial screening for first round MRI (**all extremely dense breasts**) Median (IQR) age: DM only: 54 (51–61) MRI: 55 (51–61)	Biennial	Linkage with the Netherlands Cancer Registry MRI invitation group: 6-month repeat screening
Kuhl, 2017 [31] **(Germany)**	Fp-MRI/negative screening DM (Median interval: 5 days; range 0–28 days)	Prospective observational study (2)	2005 Jan to 2013 Dec	1282/1282 (participants underwent both modalities)	MM-negative women of average breast cancer risk invited to supplemental screening at one of two academic centres. Some women also negative on ultrasound. First round data presented. Age NR	NR	Negative screens followed with MM with or without US for at least another 24 months BI-RADS 3 underwent short-term follow-up and returned to regular screening Suspicious findings underwent biopsy with MRI screening High risk lesion: biopsy/ surgical excision
Chen, 2017 [49] **(China)**	Fp-MRI/negative DM Ab-MRI/negative DM	NR (1)	2013 Jan to 2015 Mar	478/478 (participants underwent MM, FP-MRI and Ab-MRI)	MM-negative women with dense breasts invited to supplemental screening at a single institution in China Mean age: 49.3	NR	Biopsy and surgical pathology
OTHER imaging modalities							
BRAID Gilbert, 2024 [9] **(UK)**	CEM/DM (Interval median days [IQR]: 134 [91–173])	RCT (10)	2019 Sept to 2024 Mar	2035/6303	MM-negative people attending UK population breast screening at 10 centres Median (IQR) age: 56 (52–61)	Triennial	Recall cases: further imaging and biopsy if lesion confirmed Where doubt about lesion or not: repeat CEM or MRI/short term follow up offered
Starikov, 2016 [45] **(USA)**	WBS/DM One third of WBS performed with ABUS machine, two thirds performed with HHUS (Interval: same day)	Retrospective observational case–control study (1)	2013 Jan to 2013 Dec	1397/7117	People presenting for screening mammography Majority of patients >40y	Annual	List of biopsy proven screen-detected breast cancers
Starikov, 2016 [45] **(USA)**	WBS plus DBT/DM One third of WBS performed with ABUS machine, two thirds performed with HHUS (Interval: same day)	Retrospective observational case–control study (1)	2013 Jan to 2013 Dec	526/7117	People presenting for screening mammography Majority of patients >40y	Annual	List of biopsy proven screen-detected breast cancers

ˆNR, but obtained via author correspondence

[a] Number of people with supplementary modality plus DM study arm, and in the DM only arm (according to BIRADS categories D and C corresponding to heterogeneously and extremely dense breasts, respectively).

[b] Age shown if reported specifically for people with dense breasts; presented as mean, median, proportions as reported.

[c] Study was eligible for inclusion however as the intervention (supplemental modality) included synthesis mammography as well as digital breast tomosynthesis, study was not amenable to meta-analysis.

[d] Five step coding: (1) normal, (2) benign, (3) probably benign, (4) highly suspicious of malignancy, (5) malignant.

Table 2
Combined pooled estimates of the screening performance measures of four supplementary imaging modalities compared to digital mammography, with and without sensitivity analysis.

Parameter		DBT	ABUS	HHUS	MRI
CDR	Number of studies	13	6	8	6[d]
	CDR for mammography only, per 1000 exams	5.43 (3.75, 7.11)	4.52 (3.03, 6.02)	2.68 (1.77, 3.59)	-[c]
	Additional CDR, per 1000 exams	1.69 (0.81, 2.58)	2.3 (1.28, 3.33)	2.57 (0.99, 4.14)	18.92 (15.41, 22.43)
	Sensitivity analysis[a]	-	-	–	*17.23 (14.38, 20.08)*
Recall rate	Number of studies	11	5	5	3
	Recall rate for mammography only, %	12.56 (8.96,16.15)	5.97 (−0.32,12.27)	4.25 (1.37,7.12)	-[c]
	Difference in recall rate, %	−2.19 (−4.03, −0.34)	5.49 (0.85, 10.13)	6.65 (1.02, 12.27)	7.98 (4.62, 11.34)
	Sensitivity analysis[b]	*−1.94 (-3.83, -0.05)*	-	–	*9.55 (8.85,10.24)*
Biopsy rate	Number of studies	3	5	2	3
	Biopsy rate for mammography only, %	2.07 (1.57,2.57)	1.83 (0.30,3.36)	–	–
	Difference in biopsy rate, %	0.32 (0.15, 1.32)	1.62 (0.54, 2.70)	n/a	n/a

CDR, cancer detection rate; DBT, digital breast tomosynthesis; ABUS, automated breast ultrasound; HHUS, hand-held ultrasound; MRI, magnetic resonance imaging. Data in parentheses are 95 % confidence intervals.

[a] Kaiser and Chen removed for MRI sensitivity analysis [26,49].

[b] Upadhyay removed for DBT sensitivity analysis [36].

[c] These values are zero because the comparator arm in the MRI studies is 'negative mammography'.

[d] Veenhuizen was not included in the meta-analysis as this study reported the incident screening round [30]; Chen reports both abbreviated and full protocol MRI, so there are six comparisons in five studies represented in the MRI meta-analysis [49].

low risk based on randomised design or adequate control for confounders [9,18,20,23,24,26–28,30,33–38,49,51], while six studies (17 %) exhibited high risk due to non-randomised design [19,22,31,41,48,50]. Regarding reference standards, 24 studies (67 %) employed multiple verification methods [9,18,20–22,25–30,32,34–40,42,43,48,51,52]; however, ten studies (28 %) had high risk due to inadequate follow-up of participants with negative results [23,24,33,41,44–47,49,50]. Flow and timing risks were rated as unclear in 47 % [19,23,24,27,28,33,36,37,40–45,47,50,52] and high in 22 % [18,20,21,25,31,48,49] of studies due to inadequate reporting or missing data related to follow-up procedures (Appendix K).

RCT, randomised controlled trial; CBTST, Córdoba Breast Tomosynthesis Screening Trial; MBTST, Malmö Breast Tomosynthesis Screening Trial; RETomo, Reggio Emilia Tomosynthesis; PROSPR, Population-based research optimizing screening through personalized regimens; STORM, Screening with Tomosynthesis Or standard Mammograph; ASTOUND, Adjunct Screening With Tomosynthesis or Ultrasound in People With Mammography-Negative Dense Breasts; NR, not reported; DM, digital mammography; DBT, digital breast tomosynthesis; MM, mammography; BIRADS, breast imaging reporting and data system; IQR, inter-quartile range; SD, standard deviation; MRI, magnetic resonance imaging; HHUS, hand-held ultrasound; ABUS, automated breast ultrasound; BRAID, Breast Screening; Risk Adaptive Imaging for Density; CEM contrast enhanced mammography; RCT, randomised controlled trial; Ab-MRI, abbreviated MRI; Fp-MRI, full protocol MRI; DENSE, Dense Tissue and Early Breast Neoplasm Screening; EUSOBI, European Society of Breast Imaging; WBS, whole breast sonography; Meta-analyses were conducted for four supplemental imaging modalities - DBT, ABUS, HHUS, and MRI - compared with standard mammography (Table 2, Fig. 2). All supplementary modalities demonstrated higher CDR than mammography alone. In the meta-analysis, MRI showed the greatest benefit with a pooled effect size of 18·92 (95 % CI 15·41 to 22·43) additional cancers detected per 1000 screenings (Fig. 2 (i) D). A sensitivity analysis excluding small studies (<500 participants) [26,49] yielded a CDR difference for MRI of 17·23 (95 % CI 14·38 to 20·08). Screening-round analysis by Veenhuizen et al. showed a lower CDR for incident MRI screening (5·8 per 1000; 95 % CI 3·8 to 9)[30] compared to the prevalent screening round (16·5 per 1,000, 95 % CI 12·92 to 20·12) [35]. The BRAID trial reported a CDR of 19·2 (95 % CI 13·7 to 26·1) for CEM, comparable to MRI [9]. Meta-analyses of DBT, ABUS, and HHUS showed smaller but statistically significant increases in CDR: 1·69 (95 % CI 0·81 to 2·58) (Fig. 2 (i) A), 2·30 (95 % CI 1·28 to 3·33) (Fig. 2 (i) B), and 2·57 (95 % CI 0·99 to 4·14) (Fig. 2 (i) C), respectively. However, substantial heterogeneity was observed across the DBT and HHUS studies (I^2 >60 %).

Regarding recall rates, substantial heterogeneity was observed across all supplementary modalities (I^2 >90 %) (Fig. 2 (ii) A-D) DBT showed a pooled reduction of −2·19 (95 % CI -4·03 to 0·34) (Fig. 2 (ii) A) in recall rates compared with mammography alone, whereas ABUS, HHUS, and MRI (Fig. 2 (ii) B-D) demonstrated increases of 5·49 % (95 % CI 0·85 to 10·13), 6·65 % (95 % CI 1·02 to 12·27), and 7·98 % (95 % CI 4·62 to 11·34), respectively. The recall rate for CEM (9·7 %, 95 % CI 8·4 to 11) was comparable with that of MRI. Notably, definitions of recall varied across studies, contributing to the inconsistency of findings.

Regarding biopsy rates, meta-analyses were conducted only for DBT and ABUS. DBT showed no significant difference in biopsy rates versus mammography alone (pooled effect size: 0·32, 95 % CI -0·12 to 0·76) (Fig. 2 (iii) A) [24,43,44]. ABUS showed a higher rate (1·62, 95 % CI 0·54 to 2·70) with substantial heterogeneity (Fig. 2 (iii) B) [9,18,29,32,46]. For MRI, biopsy rates were 4·93 % (95 % CI 3·98 to 5·88) in the BRAID study [9]. Biopsy rates were 6·27 % (95 % CI 5·58 to 6·96) and 2·44 % (95 % CI 1·93 to 2·96) in the first [35] and second rounds [30] of the DENSE study, respectively.

Sensitivity, specificity, positive predictive value 1(number of cancers diagnosed per number of positive screens, PPV1), and biopsy proven predictive value (PPV3) were infrequently reported (Appendices F-I). Sensitivity was generally higher in supplementary imaging, except in one study where ABUS had lower sensitivity (63·6 %) than mammography-only (94·6 %) [18]. One MRI study showed high sensitivity (95·2 % [95 % CI 88·1 to 98·7]) for MRI following negative mammography [35]. A second MRI study reported sensitivity of 100 % and 88.3 % for full-protocol and abbreviated protocol MRI, respectively [49]. In the DENSE studies, MRI false positive rate declined from 79·8[35] to 26·3[30] per 1000 screenings between first and second screening rounds.

One DBT study reported interval cancer rates of 0·95 % in the supplementary arm versus 3·17 % with mammography-only [22], while the RETomo trial reported rates of 0·23 % in the supplementary group versus 0·25 % in the mammography-only group [34]. One study showed lower rates with supplemental HHUS [52] while another reported 'no interval cancers' in the HHUS/negative mammography group [51]. The DENSE trial identified four interval cancers among participants who underwent MRI and 16 among those who declined MRI, compared to 161 in the mammography group [35]. No interval cancers occurred during a two-year follow-up in the MRI study by Kuhl et al. (Appendices F-I) [31].

Cancer pathology was reported in 13 studies across all modalities. Focusing on MRI as the best-performing modality, four studies reported

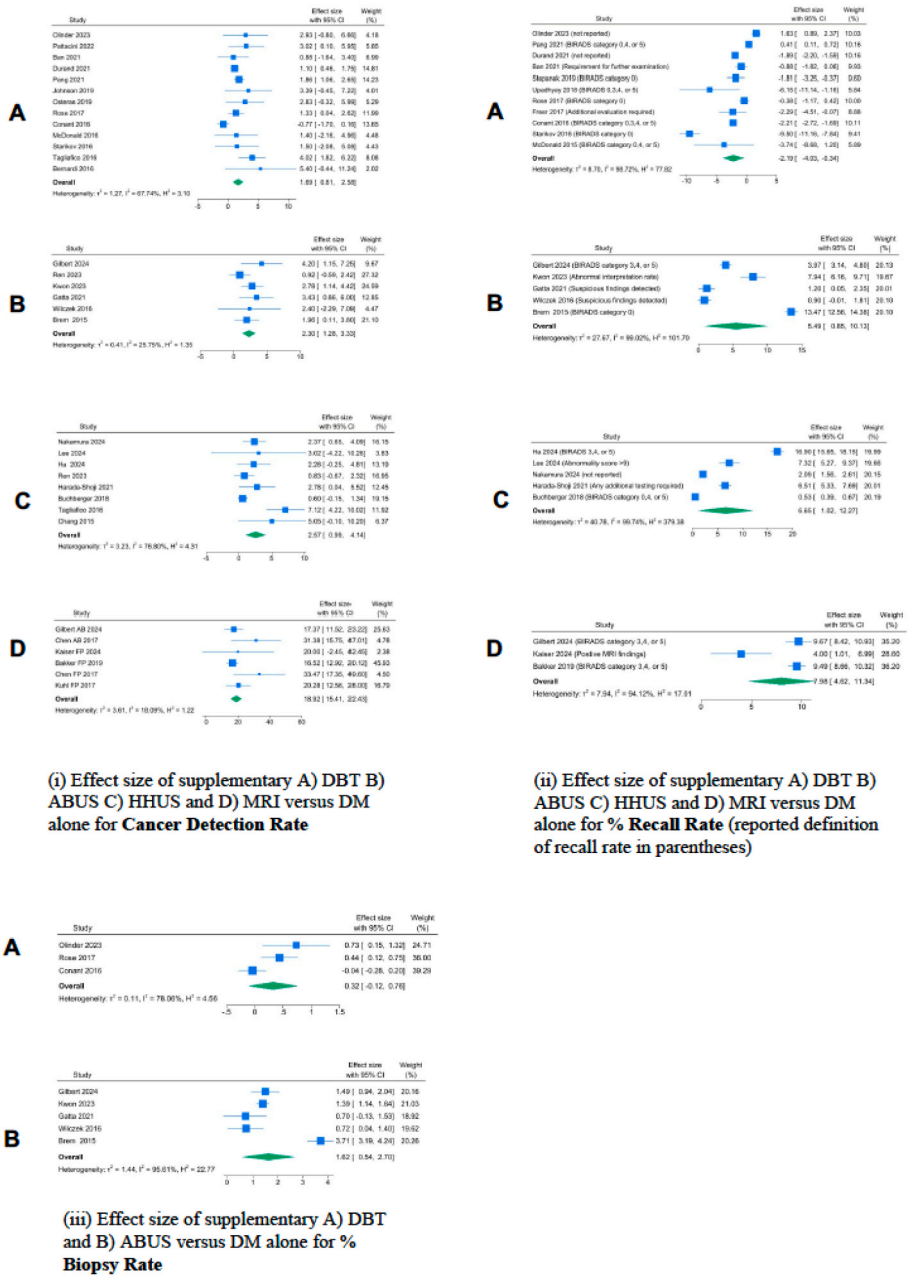

Fig. 2. Forest plots showing effect size of supplementary imaging modalities for (i) Cancer Detection Rate, (ii) Recall Rate, and (iii) Biopsy Rate (i) Effect size of supplementary A) DBT B) ABUS C) HHUS and D) MRI versus DM alone for Cancer Detection Rate (ii) Effect size of supplementary A) DBT B) ABUS C) HHUS and D) MRI versus DM alone for % Recall Rate (reported definition of recall rate in parentheses) (iii) Effect size of supplementary A) DBT and B) ABUS versus DM alone for % Biopsy Rate.

the detection of 4,[26] 14,[30] 32,[9] and 64[35] invasive cancers, respectively, in participants who'd had negative mammography. The median (IQR) tumour size detected by supplementary MRI was 1.0 cm (0.8–1.5)[9] and 0.7 cm (0.6–1.0)[30] in two studies reporting these data. A single study assessing CEM reported that 32 of 39 detected cancers were invasive, a similar performance to MRI [9].

MRI acceptance rates varied across studies and were low in some cases. Bakker et al. reported that only 59 % of invitees accepted the invitation for MRI screening [35]. In the preliminary report by Kaiser et al., 80 of 200 women (40 %) were screened but not scheduled for MRI for various reasons [26]. In the BRAID study, 188 of 2318 (8 %) women withdrew from the MRI arm due to factors such as relocation, inability to attend, personal issues, and contrast contraindications [9]. Two MRI studies did not report declinations or failures to attend MRI screening [31,49].

Nine studies reported the time taken to perform and/or interpret supplementary imaging, of which three studies reported on MRI. One study reported that supplementary full-protocol MRI took just under 10min [26]. Similarly, a second full protocol MRI study reported a performance time of less than 10min [31]. Chen et al. reported a mean (SD) interpretation time for full and abbreviated MRI protocols of 192 (44) seconds and 42 (18) seconds, respectively [49].

Regarding the safety of supplemental modalities, among the studies on MRI, Kuhl et al., [31] Chen et al., [49] and Kaiser et al. [26] did not report on adverse events or safety. In the DENSE trial, Veenhuizen et al. reported one vasovagal reaction requiring emergency department attendance, classified as a serious adverse event occurring during or immediately after the MRI examination [30]. Two additional events

were associated with contrast agent extravasation. Bakker et al. reported an incidence of 0.1 % for both adverse events and serious adverse events occurring during or immediately after MRI examination [35]. In the study published by Gilbert et al. one case of extravasation was reported (0.5 events per 1000 examinations), with no other adverse events noted [9]. In contrast, Gilbert et al. observed 24 iodinated contrast reactions in the CEM group comprising 17 minor, six moderate, and one severe reaction along with three cases of extravasation [9]. The authors did not report whether the observed difference in adverse reactions to intravenous contrast media between MRI (0.5 in total per 1000 examinations) and CEM (13.3 in total per 1000 examinations) was statistically significant.

The parallel systematic review of economic models assessing enhanced mammographic screening for individuals with dense breasts identified 12 modelling studies [53–64]. These included ten cost-utility analyses (CUA) [53–56,59–64], and two cost-effectiveness analyses (CEA) [57,58], primarily from the US, employing diverse decision-analytic approaches such as microsimulation, discrete event simulation (DES), and hybrid Markov or decision tree models (Appendix M). MRI was the most commonly assessed supplemental modality. Five of seven MRI modelling studies found it potentially cost-effective [53, 56,57,59,62], particularly in risk-stratified strategies or as a replacement for mammography in women with extremely dense breasts (Appendix P). Some studies conducted in the Netherlands supported MRI every four years for women with BI-RADS D density [56], and Ab-MRI biennially for women aged 50–65 with BI-RADS C or D density [57], both reporting acceptable incremental cost-effectiveness ratio (ICERs) under the pre-specified €20,000 per life-year gained (LYG) threshold. In contrast, UK [64] and Canadian [61] studies found minimal QALY gains and high ICERs, deeming MRI or Ab-MRI not cost-effective. Cost-effectiveness of MRI was highly sensitive to assumptions about mammography sensitivity, age-related density decline, and utility weights. Some economic models reported Ab-MRI to be cost-effective when added after a negative result for annual mammography, but these results were often driven by optimistic assumptions of near-perfect utility for healthy or treated individuals, potentially inflating QALY gains. CEM, though less frequently evaluated, yielded mixed results. One UK-based study suggested that a screening strategy combining mammography and CEM could offer a more cost-effective approach than MRI-based screening strategies (Appendix Q) [64]. Another study found CEM less favourable compared to Ab-MRI or ABUS (Appendix Q) [53]. Quality assessment using the Philips checklist showed variable reporting standards, with scores ranging from 38 % to 89 % (Appendix O). Only four studies calibrated their models against independent data [53–56], and many relied on pre-existing frameworks (e.g., MISCAN, CISNET, SiMRiSc, Appendix M). Utility assumptions strongly influenced ICERs; perfect or near-perfect values (1·0[59,62] or 0·99[59]) for individuals without cancer or post-treatment, biased the results toward cost-effectiveness. Characteristics of economic analyses (Appendix O), MRI summary results (Appendix P) and summary results of various supplemental modalities used alongside MRI and CEM (Appendix Q) are provided in the supplementary file.

4. Discussion

Standard mammography often fails to detect breast cancer in individuals with dense breasts; notwithstanding, the accuracy of screening interpretation is also influenced by factors such as the technical quality of the mammogram and the radiologist's level of experience. In our review, DBT detected 1-2 additional cancers per 1000 screenings, while both ABUS and HHUS identified 2-3 additional cancers per 1000 screenings compared to mammography alone. MRI emerged as a superior imaging modality, detecting nearly 19 additional cancers per 1000 screenings. Even after excluding smaller studies, MRI consistently identified more than 17 additional cancers per 1000 screenings. In a single study, CEM detected 19 additional cancers per 1000 screenings, suggesting its performance may be comparable to MRI in average-risk individuals with dense breasts [9]. This highlights CEM's promise as a supplementary tool, particularly because it has traditionally been used in higher-risk populations.

While CDR is a key outcome measure, breast screening programmes also commonly report the 'referral to assessment rate' (RAR) – often referred to as recall rate – to mitigate the psychological burden and unnecessary investigations associated with false-positive findings. UK target recall rates are set at under 7 % for prevalent screenings and below 5 % for incident screenings [65]. Although elevated recall rates are undesirable, they may correlate with lower interval cancer rates [66], suggesting a minimal threshold may be important to optimise screening benefits. Our meta-analyses showed recall rates were broadly similar for ABUS, HHUS, and MRI, despite MRI meta-analysis having a much higher CDR, which typically aligns with increased recall rate. Studies of prevalent screenings [9,31,35] reported higher recall rates than the study by Veenhuizen [30] on incident screenings, indicating that both CDR and recall rate may decline over time. Disparities in how 'recall' was defined likely contributed to the substantial heterogeneity and wide confidence intervals across studies. Inclusion of BI-RADS 0 in recall criteria in several studies complicated direct comparisons. In contrast, MRI studies used more consistent definitions, enhancing the reliability of the meta-analysis results.

Interval cancer rates were rarely reported, but two MRI studies provided relevant data [31,35]. One study found an interval cancer rate of 2·5 per 1000 screenings in the MRI group, versus 5·0 per 1000 screenings in the mammography alone group [35]. Notably, in this study, only 59 % of participants accepted MRI screening, highlighting potential challenges with acceptability and implementation. Among those who declined, the interval cancer rate was 4·9 per 1000 screenings compared to 0·8 per 1000 screenings among those who underwent MRI. A second MRI study reported no interval cancers after over two years of follow-up among participants who had supplemental MRI after negative mammography or negative mammography and ultrasound, albeit in a small population sample [31].

Sensitivity and specificity values were inconsistently reported, hampering the ability to conduct further analysis. Where available, sensitivity was higher for supplementary imaging than for mammography alone, and specificity often exceeded 90 %, indicating reliable performance.

Quality assessment of the modelling studies revealed a potential risk of bias related to flow and timing. Delays between tests were common, likely due to logistical challenges such as limited imaging access, specialist expertise and costs. For example, median intervals between imaging tests ranged from 8 to 20 weeks across MRI studies [9,30,35], while the study by Kaiser et al. did not report the median interval between tests but excluded delays over two months to avoid misclassifying interval cancers [26]. Similar delays were observed in the BRAID study: 16 weeks (IQR 11–21) for ABUS and 19 weeks (IQR 13–25) for CEM, indicating systemic scheduling constraints [9].

Economic modelling studies produced mixed results. While MRI showed potential cost-effectiveness, particularly for younger women with dense breasts, results were highly sensitive to modelling assumptions. Risk-stratified screening approaches yielded inconsistent outcomes even for studies conducted for the same country and perspective [63,64], driven by substantial differences in QALY estimates.

4.1. Implications for practice and policy

Both MRI and CEM showed higher CDR compared to DBT, ABUS, and HHUS in individuals with dense breast tissue. Given their superior performance MRI, and potentially CEM, should be considered in future screening policy reviews for this population. Further research directly comparing MRI to CEM in women with dense breasts is needed, because current ongoing studies, including CMIST (completion expected in 2025) and C-MERIT (late 2026), assess CEM in screening contexts but do

not offer head-to-head comparisons. Our economic evaluation also highlights the need for standardised models and context-specific analyses to support informed screening policy decisions.

MRI and CEM require different types of contrast media with distinct safety profiles. The risk of immediate adverse reactions to gadolinium-based contrast agent (GBCA, used in MRI) has been reported to be approximately 6–9 per 10,000 examinations [67], whereas for modern non-ionic, low-osmolality iodinated contrast (used in CEM) the risk of hypersensitivity reaction may occur in up to 1 % of patients [68]. The administration of either agent in a screening setting introduces a potential risk of harm that must be carefully weighed over and above the established potential harm of screening, such as overdiagnosis and overtreatment. Three studies on supplemental MRI screening reported adverse events related to vasovagal reactions or contrast extravasation. In the study by Gilbert et al., a higher rate of adverse reactions was observed in the CEM arm compared with the MRI arm which might be consistent with what would be expected in clinical practice [9].

4.2. Strengths and weaknesses

This review included both retrospective studies and those with randomised or paired designs, which may potentially introduce selection bias. To mitigate this, we excluded studies involving pre-selected high-risk populations, such as individuals with family history or prior breast cancer, ensuring our focus remained on average-risk individuals with dense breasts. Supplemental screening may be more feasible for individuals with extremely dense breasts, representing less than 10 % of the screening population, rather than for the broader group with dense and extremely dense tissue (nearly 50 % of the screening population). However, we did not evaluate whether supplemental imaging modalities are more effective for those with extremely dense breasts. Pooled estimates reflect relative differences in outcomes, rather than absolute detection values. Importantly, our review incorporated recent literature, including studies published up to November 2024, ensuring the inclusion of the most up-to-date evidence in this rapidly evolving field.

5. Conclusions

Standard mammography alone is insufficient for detecting breast cancer in individuals with dense breasts. While adjunctive modalities such as ABUS, HHUS, and DBT offer modest incremental improvements, they still miss many cancers. MRI substantially increases CDR, and emerging evidence suggests CEM may also be a valuable supplemental screening option. Overall, quality assessment revealed methodological variability, delays in imaging access, and underrepresentation of women with extremely dense breasts. To inform effective screening strategies, future research must address the current key evidence gaps, particularly the comparative effectiveness of CEM versus MRI and their cost-effectiveness.

CRediT authorship contribution statement

Sinéad N. Duggan: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Data curation. **Mohammad Azharuddin:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Data curation. **Rodolfo Hernández:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization. **Clare Robertson:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Data curation. **David Cooper:** Writing – review & editing, Visualization, Formal analysis. **Emma McCall:** Writing – review & editing, Validation, Investigation. **Paul Manson:** Writing – review & editing, Resources, Methodology. **Gianni Virgili:** Writing – review & editing, Supervision, Methodology. **Mike Clarke:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Shaun Treweek:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Miriam Brazzelli:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Ethical approval

Not applicable.

Data sharing

This is an evidence synthesis; all quantitative data are presented in the text or contained within tables, figures, and supplementary material. No new data suitable for data sharing have been created in the preparation of this synthesis. All queries should be submitted to the corresponding author for consideration.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT-4o to shorten sections of the manuscript and to prepare an initial draft of the summary to help meet the word count limit. AI was not used to generate new content. All original text was written by a human author, and the ChatGPT-generated summary was derived solely from human-written material. After using this tool/service, the final versions of the summary was reviewed by all authors and differs significantly from the initial ChatGTP-generated draft, and the authors take full responsibility for the content of the publication.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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