research

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ORIGINAL RESEARCH Longitudinal study

Trajectories of breast density change over time and subsequent breast cancer risk

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Cite this as: *BMJ* 2024;387:e079575
Find this at doi: 10.1136/bmj-2024-079575

Study question How does breast density change over time and what are the associations between trajectories of breast density change and subsequent risk of breast cancer?

Methods This retrospective cohort study used data from the Korean national breast cancer screening programme to identify women aged ≥40 years who had undergone four biennial mammograms between 2009 and 2016. Breast cancer development in these women was determined to 31 December 2021. Breast density was assessed using the four category Breast Imaging Reporting and Data System classification. Group based trajectory modelling was performed to identify the trajectories of breast density, and Cox proportional hazard models were used to assess the associations between trajectories and breast cancer outcomes after adjusting for covariates such as body mass index, family history of breast cancer, and menopausal status.

Study answer and limitations Among a cohort of 1 747 507 women (mean age 61.4 years), five breast density trajectory groups were identified. Group 1 included women with persistently low density breasts, group 2 included those with low density breasts at baseline but increased breast density over time, and groups 3-5 included women with denser breasts, with a slight decrease in density over time. Women in group 2 had a 1.60-fold (95% confidence interval 1.49-fold to 1.72-fold) increased risk of breast cancer compared with those in group 1. Women in groups 3-5 had higher risks compared with those in group 1, with adjusted hazard ratios of 1.86 (1.74 to 1.98), 2.49 (2.33 to 2.65), and 3.07 (2.87 to 3.28), respectively. Similar results were observed across different age groups, regardless of changes in menopausal status or body mass index. Limiting the population to women with four screening cycles reduced the representativeness and validity of the study because only healthy women with good adherence are likely to attend regular screenings.

What this study adds Five distinct groups of women with similar trajectories of breast density change over time were identified. Future risk of breast cancer was found to vary in these groups, with increasingly dense or persistently dense breasts associated with a higher risk.

Funding, competing interests, and data sharing Funded by the National Research Foundation of Korea. No competing interests declared. Data provided by the Korean National Health Insurance Sharing Service (http://nhiss.nhis.or.kr) through a data use agreement.

Dementia, survival rates, and nursing home admissions

ORIGINAL RESEARCH Systematic review and meta-analysis

Time to nursing home admission and death in people with dementia

Brück CC, Mooldijk SS, Kuiper LM, et al

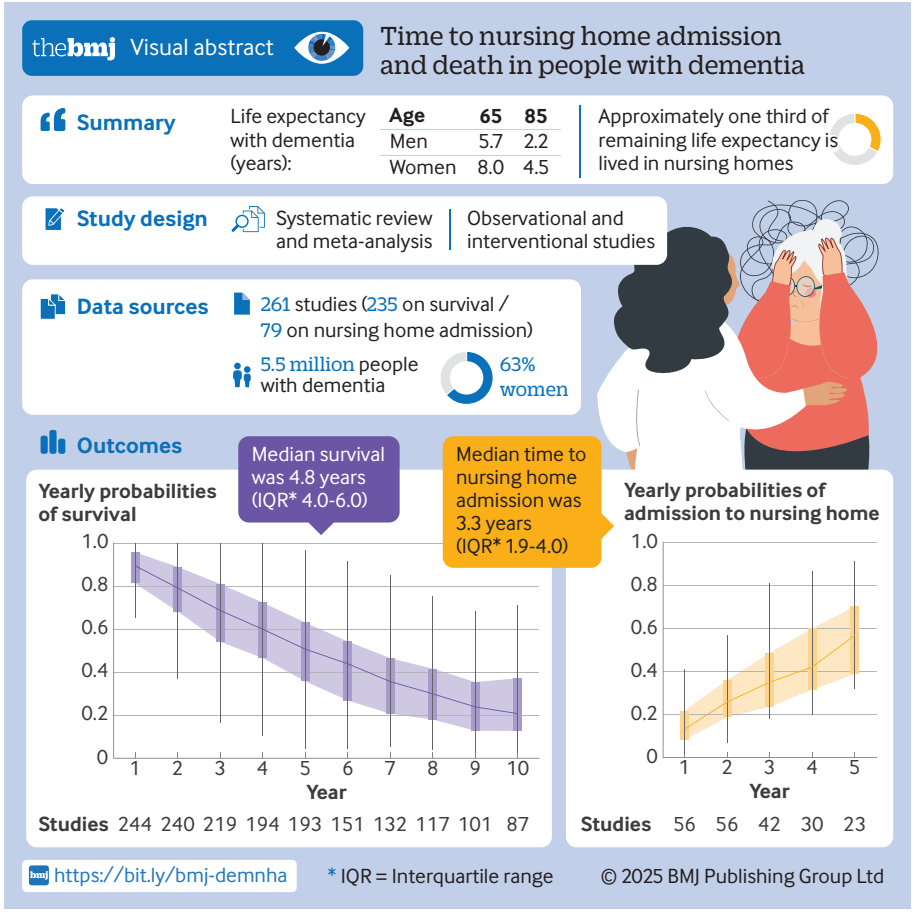
Cite this as: *BMJ* 2025;388:e080636
Find this at doi: 10.1136/bmj-2024-080636

Study question What is the available evidence on time to nursing home admission and death among people with dementia, and what are the prognostic indicators?

Methods Medline, Embase, Web of Science, Cochrane, and Google Scholar were searched from inception to 4 July 2024 for longitudinal studies on survival or admission to nursing home in people with dementia that included at least 150 participants followed-up for a minimum of one year after diagnosis. The main outcome measures were median survival, yearly survival probabilities, median time to nursing home admission, and yearly probabilities of nursing home admission, calculated as weighted averages. Prognostic indicators were assessed using meta-regressions. Risk of bias was assessed using a modified Newcastle-Ottawa scale.

Study answer and limitations Of 19 307 identified articles, 261 eligible studies were included. Of those, 235 reported on survival among 5 553 960 participants and 79 reported on nursing home admission among 352 990 participants. Median survival from diagnosis appeared to be strongly dependent on age, ranging from 8.9 years at mean age 60 for women to 2.2 years at mean age 85 for men. Women overall had shorter survival than men (mean difference 4.1 years (95% confidence interval 2.1 to 6.1)), which was attributable to later age at diagnosis in women. Median survival was 1.2 to 1.4 years longer in Asia than in the US and Europe, and 1.4 years longer for people with Alzheimer's disease compared with other types of dementia. Compared with studies before 2000, survival was longer in contemporary clinic based studies (P_{trend}=0.02), but not in community based studies. Taken together, variation in reported clinical characteristics and study methodology explained 51% of heterogeneity in survival. Median time to nursing home admission was 3.3 years (interquartile range 1.9 to 4.0 years). 13% of people were admitted in the first year after diagnosis, increasing to 57% at five years, but few studies appropriately accounted for competing mortality risk when assessing admission rates. Various potentially relevant predictor variables were inconsistently reported across the studies, such as measures of socioeconomic status, race, disease severity, and comorbidity, which limited meta-regression analyses.

What this study adds The average life expectancy of people with dementia at time of diagnosis ranged from 5.7 years at age 65 to 2.2 at age 85 in men and from 8.0 to 4.5, respectively, in women. About one third of remaining life expectancy was lived in nursing homes, with more than half of people moving to a nursing home within five years after a dementia diagnosis. Prognosis after a dementia diagnosis is highly dependent on personal and clinical characteristics, offering potential for individualised prognostic information and care planning.



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Funding, competing interests, and data sharing
Supported by a research fellowship of the Alzheimer's Association. No competing interests declared. Detailed extracted data are available upon reasonable request.

Study registration PROSPERO CRD42022341507.

For clinicians it is an important and demanding task to inform patients with dementia and their relatives about the prognosis. As with malignant diseases, discussing remaining life expectancy and time to death is a delicate matter. But it is even more challenging to provide information about the timeline for dependency and need for nursing home care because many factors are involved, not only the type of dementia, sex, and age of patients, but also comorbidities, lifestyle, and socioeconomic and cultural factors. Some patients seek all available information about their prognosis, whereas others prefer to know less, and the emotional response to information on the dementia diagnosis and prognosis varies substantially, from catastrophic to pragmatic. Additionally, a substantial discrepancy can exist between what patients and their relatives want in terms of information.

The previous reviews on dementia related survival[1 2] and nursing home admission were published more than a decade ago,[3] so the study by Brück and colleagues is a welcome update.[4] As in the previous reviews,[1 2] Brück and colleagues found survival to be inversely associated with age, that type of dementia mattered (with highest survival in people with Alzheimer's disease), and survival was increased in clinic based versus community based studies, mostly attributed to the tendency for community dwelling participants to be older. Another influential factor might be differences in referrals related to socioeconomic status, as people referred to memory clinics tend to have a higher socioeconomic status and therefore better survival.[5]

Informing prognosis

Even with a solid knowledge base, differences in choice of survival measure could result in confusion about prognosis. Studies focusing on survival tend to highlight the better survival with early versus late onset dementia,[2] whereas studies focusing on loss in life expectancy emphasise the much higher loss associated with early onset dementia.[1] Brück and colleagues acknowledge this and report on both measures, with a reported median survival of 8.9 years for women with a dementia diagnosis at age 60 and 4.5 years at age 85, and with numbers for men slightly lower. The corresponding losses in life expectancy were 13 years at age 65, three to four years at age 80, and two years at age 85. With this information, clinicians could inform younger female patients that their expected survival would be a bit better than that for older peers but that compared with women without a dementia diagnosis, they could expect a shorter life, which might have implications for matters such as planning for the remaining years.

JIM VARNEY/SPL

Older age was associated with higher probabilities of mortality and transitions to more care intensive states

Brück and colleagues' estimates on time to nursing home admission were, however, less reliable and therefore less useful for informing patients and carers. This was due to both methodological challenges and multiple factors that affect nursing home admission. The pooled estimate in their study suggested that one third of remaining life expectancy after a dementia diagnosis was spent in a nursing home, with more than half of patients moving to this setting within five years of diagnosis. This is disheartening information to share with patients, and we believe these results may overestimate the risk of nursing home admission. Only 9% of the studies in nursing homes accounted for competing risk, so these estimates should be interpreted with caution. In the previous review, the authors concluded that research activities in this area lacked methodological strength,[3] which is still true. Thus, we welcome more rigorous studies, taking competing risk of death into account. Furthermore, pooled averages might be of less relevance than country specific estimates, or more geographically finely granulated estimates.

Clinical implications

Brück and colleagues suggest that multistate models that take mortality into account could shed light on transition probabilities to nursing homes. A Dutch study reporting on transition probabilities between no formal care, home care, institutional care, and death showed that older age was associated with higher probabilities of mortality and transitions to more care intensive states.[6] Furthermore, men had a lower probability of transitioning from no formal care to nursing home care and a higher probability of mortality when receiving nursing home care or institutional care compared with women. Also, in a Norwegian multistate study of people with dementia,[7] men had lower rates of nursing home admission owing to higher mortality, and cohabitating with a partner reduced the likelihood of admission.

Although the understanding of survival with dementia has advanced substantially, the complexities of predicting the timeline for nursing home admission persist. To enhance future healthcare services and optimise quality of life for people with dementia and their families, it is crucial that we continue to strive for more precise, context sensitive insights.

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Cite this as: *BMJ* 2025;388:q2677

Find the full version with references at http://dx.doi.org/10.1136/bmj.q2677

Environmentally friendly inhaler regimens for COPD

ORIGINAL RESEARCH New user cohort study

Comparative effectiveness and safety of single inhaler triple therapies for chronic obstructive pulmonary disease

Feldman WB, Suissa S, Kesselheim AS, et al

Cite this as: *BMJ* 2024;387:e080409
Find this at doi: 10.1136/bmj-2024-080409

Study question What is the comparative effectiveness and safety of budesonide-glycopyrrolate-formoterol, a twice daily metered dose inhaler, versus fluticasone-umeclidinium-vilanterol, a once daily dry powder inhaler, in patients with chronic obstructive pulmonary disease (COPD) treated in routine clinical practice?

Methods Data were obtained from a longitudinal US commercial claims dataset. Adults aged 40 years or older with a diagnosis of COPD who had newly initiated budesonide-glycopyrrolate-formoterol or fluticasone-umeclidinium-vilanterol were included in the study between 1 January 2021 and 30 September 2023. The primary outcome was first moderate or severe COPD exacerbation (effectiveness) and first admission to hospital for pneumonia (safety) while receiving treatment. Potential confounders were measured in the 365 days before cohort entry and included in the propensity scores. The primary analysis was a 1:1 propensity score matched analysis. Hazard ratios and 95% confidence intervals were estimated using a Cox proportional hazards regression model.

Study answer and limitations The study cohort included 20 388 propensity score matched pairs of new users initiating single inhaler triple therapy. Patients who received budesonide-glycopyrrolate-formoterol had a 9% higher incidence of a first moderate or severe COPD exacerbation (hazard ratio 1.09 (95% confidence interval 1.04 to 1.14)) compared with the dry powder inhaler fluticasone-umeclidinium-vilanterol and no difference in risk of pneumonia requiring hospital admission (1.00 (0.91 to 1.10)). The authors suggest that guidelines and insurance formularies may consider prioritising dry powder inhalers over metered dose inhaler triple therapy for treating patients with COPD.

COMMENTARY Consider patient characteristics when making treatment decisions

Triple therapy of an inhaled corticosteroid, long acting β_2 agonist (LABA), and long acting muscarinic antagonist (LAMA) is more effective in reducing the annual rate of exacerbations compared with LABA-LAMA or LABA-inhaled corticosteroid in patients with chronic obstructive pulmonary disease (COPD), a history of exacerbations, and high symptom burden in pivotal randomised trials.[1-4] However, this treatment combination is associated with a 1.52-fold to 1.96-fold increased incidence of pneumonia.[3 4] Triple therapies are available with different LABA, LAMA, and inhaled corticosteroid drugs, and in different inhaler devices such as dry powder inhalers and propellant-containing metered dose inhalers. Given interclass differences in pharmacological and physiochemical properties of LABAs, LAMAs, and inhaled corticosteroids,[5 6] different triple therapy combinations may lead to varying clinical outcomes. The release of hydrofluoroalkanes from metered dose inhalers has been linked to green gas emissions; replacing metered dose inhalers with dry powder inhalers has been advocated to reduce the carbon footprint of healthcare.[7] However, head-to-head comparisons of LABA-LAMA-inhaled corticosteroid triple therapy combinations and metered dose inhaler versus dry powder inhaler in people with COPD remain limited.

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What did the authors find?

In their study, Feldman and colleagues assessed the comparative effectiveness and safety of a single metered dose inhaler budesonide-glycopyrrolate-formoterol taken twice daily versus a single dry powder inhaler fluticasone-umeclidinium-vilanterol taken once daily. Their study was of 20 388 matched pairs of patients with COPD using a US commercial healthcare claims database.[8] The authors adopted a rigorous new user, active comparator, and propensity score matching cohort study. They found that the metered dose inhaler budesonide-glycopyrrolate-formoterol was associated with a 9% higher incidence of first moderate or severe exacerbations (hazard ratio 1.09 (95% confidence interval 1.04 to 1.14)) compared with the dry powder inhaler fluticasone-umeclidinium-vilanterol and no difference in risk of pneumonia requiring hospital admission (1.00 (0.91 to 1.10)). The authors suggest that guidelines and insurance formularies may consider prioritising dry powder inhalers over metered dose inhaler triple therapy for treating patients with COPD.

Feldman and colleagues' findings should be interpreted in the context of potential limitations. The observed differences in exacerbation risk may be attributable to variations in both inhalation devices and drug moieties of the two triple therapies. Although the authors addressed unmeasured confounding using the high dimensional propensity score matching and E-value method, the potential impact of unmeasured lung function cannot be fully ruled out. The generalisability of the study may be limited because the median treatment duration was short (113 days

1.09 (95% confidence interval 1.04 to 1.14); number needed to harm 38) compared with patients who received fluticasone-umeclidinium-vilanterol, and an identical incidence of first admission to hospital with pneumonia (1.00 (0.91 to 1.10)). A limitation of the study was that only two single inhaler triple therapies available on the US market were analysed.

What this study adds Budesonide-glycopyrrolate-formoterol was not associated with improved clinical outcomes compared with fluticasone-umeclidinium-vilanterol. Given the added climate impact of metered dose inhalers, health systems seeking to decrease use of these products may consider steps to promote further prescribing of fluticasone-umeclidinium-vilanterol compared with budesonide-glycopyrrolate-formoterol in people with COPD.

COPD exacerbations and admission to hospital for pneumonia in matched cohort of patients receiving single inhaler triple therapy

Outcomes	Events/1000 person years		Hazard ratio (95% CI)	Risk difference at 365 days, % (95% CI)	NNH (95% CI)*
	Fluticasone-umeclidinium-vilanterol	Budesonide-glycopyrrolate-formoterol			
COPD exacerbation:					
Moderate or severe	482.8	535.7	1.09 (1.04 to 1.14)	2.6 (0.8 to 4.4)	38
Moderate	451.1	489.6	1.07 (1.02 to 1.12)	1.9 (0.1 to 3.6)	54
Severe	41.9	54.4	1.29 (1.12 to 1.48)	1.0 (0.1 to 1.9)	97
Hospital admission for pneumonia	103.9	106.0	1.00 (0.91 to 1.10)	0.4 (−0.6 to 1.3)	NA

CI=confidence interval; COPD=chronic obstructive pulmonary disease; NA=not available; NNH=number needed to harm.
*Calculated as 1/risk difference at 365 days of follow-up and only when 95% CIs for the risk difference excluded the null.

Funding, competing interests, and data sharing Funded by a grant from the National Heart, Lung, and Blood Institute to WBF. See full paper on bmj.com for competing interests. Data use agreements do not permit sharing of source data or derivative analytical cohorts.

Study registration Center for Open Science Real World Evidence Registry (https://osf.io/6gdyp/).

for dry powder inhaler and 88 days for metered dose inhaler triple therapy), 40% of the analysed patients had asthma claims in the previous year, and 70% of people who were using a metered dose inhaler were excluded through 1:1 propensity score matching.

Choosing inhaler type

With increasing global efforts to reduce greenhouse emissions, Feldman and colleagues' study provides assurance to patients and clinicians when choosing a dry powder inhaler over a metered dose inhaler of LABA-LAMA-inhaled corticosteroid in a single inhaler, if clinically appropriate and preferred, with respect to its effectiveness, safety, and carbon footprint. However, clinicians should be cautious about patient characteristics when deciding between metered dose inhalers and dry powder inhalers. Many patients with COPD do not produce enough inspiratory force to overcome the device resistance of dry powder inhalers and disperse the powder into particles.[9 10] For this reason, patients with COPD with a reduced respiratory capacity could still benefit from

Incorporating an environmentally friendly inhaler into practice needs to be weighed against clinical appropriateness and patients' preferences

using a metered dose inhaler. Proper technique of inhaler use is another major barrier. In a survey study, 15.4-46.9% of participants made critical errors in handling their metered dose inhaler or dry powder inhaler, which were associated with COPD exacerbations.[11] For patients who would like to switch from metered dose inhaler budesonide-glycopyrrolate-formoterol to dry powder inhaler fluticasone-umeclidinium-vilanterol, clinicians and pharmacists are strongly recommended to provide education on proper inhaler techniques and to periodically assess patients' abilities in handling inhalers.

For future research, the effectiveness and safety assessment of metered dose inhaler versus dry powder inhaler triple therapy needs to be conducted while controlling intraclass differences of individual drugs, such as comparing the metered dose inhaler counterpart, and accounting for patients' inspiratory flow rates if possible. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy recommends initiating triple therapy as an initial pharmacological therapy in patients with at least two moderate exacerbations or one severe exacerbation requiring admission to hospital in the previous year (GOLD group E) and a blood eosinophil count of at least 300 cells/µL.[12] However, pivotal trials and Feldman and colleagues' study included patients with longstanding COPD who had received previous pharmacological treatments, and therefore triple therapy was not the first inhaled therapy. To fill this gap, future research can also assess the comparative effects of different triple therapy combinations in patients who have not received any inhaled therapy previously. Despite ongoing debate about whether all patients in GOLD group E should receive triple therapies,[13 14] future studies are urgently needed. These studies should have sufficient statistical power for assessing the comparative effects of triple therapy combinations in patients with COPD with varying eosinophil concentrations and potentially different future exacerbation risks, such as people with a history of one moderate or one severe exacerbation and patients categorised as GOLD group E.

Feldman and colleagues' findings provide a starting point for understanding the impact of different triple therapy combinations on exacerbation and pneumonia risks in patients with COPD, potentially influenced by differences in inhaler devices in real world settings. Incorporating an environmentally friendly inhaler into practice needs to be weighed against clinical appropriateness and patients' preferences. More evidence is needed to assess clinical outcomes associated with metered dose inhalers versus dry powder inhalers and to develop strategies to safely transition patients with COPD from metered dose inhaler to dry powder inhaler based triple therapy.

Cite this as: *BMJ* 2024;387:q2825

Find the full version with references at http://dx.doi.org/10.1136/bmj.q2825

Effectiveness of shared decision making strategies for stroke prevention among patients with atrial fibrillation

Ozanne EM, Barnes GD, Brito JP, et al; on behalf of the STEP-UP Writing Group

Cite this as: *BMJ* 2025;388:e079976
Find this at doi: 10.1136/bmj-2024-079976

Study question Can patient decision aids and encounter decision aids promote high quality shared decision making for stroke prevention in patients with non-valvular atrial fibrillation?

Methods This multicentre cluster randomised controlled trial was conducted at six academic medical centres in the US. Patient participants were aged 18 and older, with a diagnosis of non-valvular atrial fibrillation and at risk of stroke (CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65-74, and sex category (female)) ≥1 for men, ≥2 for women) and scheduled for a clinical appointment to discuss stroke prevention strategies. Clinician participants were those who managed stroke prevention strategies for participating patients. Patients were randomised to use a patient decision aid or usual care; clinicians were randomised to use an encounter decision aid or usual care with all participating patients. Primary outcome measures were quality of shared decision making measured by OPTION12 (an observer based score derived from the clinical encounter, transformed to values 0-100, with higher scores representing greater shared decision making), knowledge of atrial fibrillation and its management, and decisional conflict.

Study answer and limitations Patients who received both the encounter decision aid and the patient decision aid had improved observer assessed quality of shared decision making (adjusted mean difference 12.1 (95% confidence interval (CI) 8.0 to 16.2); P<0.001), improved objectively assessed knowledge (odds ratio 1.68 (95% CI 1.35 to 2.09); P<0.001), and reduced patient reported decisional conflict (adjusted mean difference −6.3 (95% CI −9.6 to −3.1); P<0.001) compared with those receiving usual care. Patients less adept at using digital tools may have been more reluctant to enrol in a trial using web based decision aids, limiting the applicability of the findings.

What this study adds This study found that the use of a patient decision aid or an encounter decision aid individually or in combination yielded better shared decision making outcomes than usual care.

Funding, competing interests, and data sharing
Funded by the American Heart Association and the Patient-Centered Outcomes Research Institute. No competing interests declared. Deidentified data will be posted to ClinicalTrials.gov according to the sponsors' requirements and timeline; additional data may be shared on reasonable request.

Trial registration ClinicalTrials.gov NCT04357288.

Group comparisons for co-primary outcomes

	OPTION12 score			Knowledge score		Decisional conflict score		
Comparison*	Estimated difference (CI)†	SE	P value‡	Odds ratio (CI)†	P value‡	Estimated difference (CI)†	SE	P value‡
Primary comparisons								
EDA and PDA *v* control	12.1 (8.0 to 16.2)	2.09	<0.001	1.68 (1.35 to 2.09)	<0.001	-6.3 (−9.6 to −3.1)	1.67	<0.001
Secondary comparisons								
EDA *v* control	12.9 (8.6 to 17.1)	2.07	<0.001	1.41 (1.11 to 1.79)	0.003	−5.8 (−9.3 to −2.4)	1.68	<0.001
PDA *v* control	3.8 (1.1 to 6.4)	1.02	<0.001	1.68 (1.24 to 2.28)	<0.001	−2.6 (−6.8 to 1.6)	1.63	0.11
Exploratory comparisons								
EDA *v* PDA	9.1 (5.0 to 13.2)	2.07	<0.001	0.84 (0.64 to 1.10)	0.20	−3.2 (−6.6 to 0.1)	1.72	0.06
EDA and PDA *v* EDA	−0.8 (−3.0 to 1.4)	1.12	0.48	1.19 (0.95 to 1.49)	0.14	−0.5 (−3.9 to 2.9)	1.72	0.76
EDA and PDA *v* PDA	8.3 (4.3 to 12.4)	2.07	<0.001	1.00 (0.77 to 1.29)	0.99	−3.7 (−7.1 to −0.4)	1.72	0.03

CI=confidence interval; EDA=encounter decision aid; PDA=patient decision aid; SE=standard error.
*Treatment comparisons under linear mixed effects model (for decisional conflict and OPTION12) or generalised linear mixed effects model (for knowledge score).
†95% CI for primary and exploratory comparisons; 96% CI for EDA *v* control; 99% CI for PDA *v* control.
‡Statistical significance indicated by P<0.05 for primary and exploratory comparisons, P<0.04 for EDA *v* control, and P<0.01 for PDA *v* control.