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Health Technology Assessment

Volume 25 • Issue 1 • January 2021

ISSN 1366-5278

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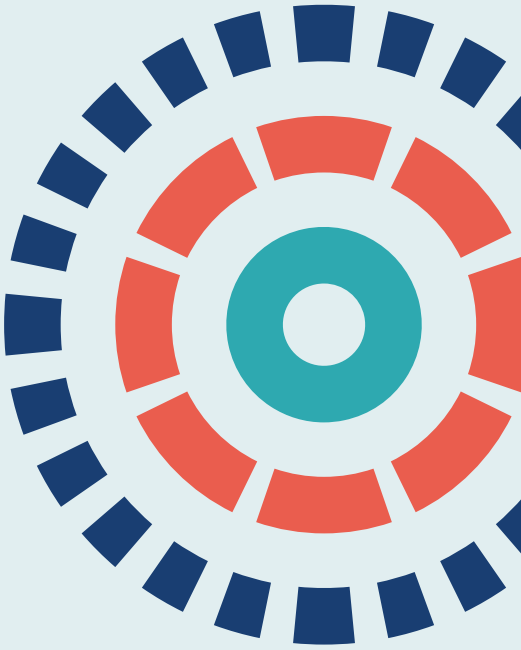

DOI 10.3310/hta25010

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Declared competing interests of authors: George M Savva reports grants from the National Institute for Health Research Health Technology Assessment programme during the conduct of the study (for Health Services and Delivery Research 14/70/96). Yoon K Loke reports personal fees from Thame Laboratories (London, UK) outside of the submitted work. Clive Ballard reports grants and personal fees from Acadia Pharmaceuticals (San Diego, CA, USA) and Lundbeck (Copenhagen, Denmark), and personal fees from Roche (Basel, Switzerland), Otsuka Pharmaceutical (Tokyo, Japan), Novartis (Basel, Switzerland), Eli Lilly and Company (Indianapolis, IN, USA) and Pfizer Inc. (Pfizer Inc., New York, NY, USA).

Published January 2021
DOI: 10.3310/hta25010

This report should be referenced as follows:

Richardson K, Savva GM, Boyd PJ, Aldus C, Maidment I, Pakpahan E, *et al*. Non-benzodiazepine hypnotic use for sleep disturbance in people aged over 55 years living with dementia: a series of cohort studies. *Health Technol Assess* 2021;**25**(1).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.370

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics, Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 14/221/02. The contractual start date was in June 2016. The draft report began editorial review in November 2018 and was accepted for publication in July 2019. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

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Abstract

Non-benzodiazepine hypnotic use for sleep disturbance in people aged over 55 years living with dementia: a series of cohort studies

Kathryn Richardson,[1] George M Savva,[1,2] Penelope J Boyd,[1,3] Clare Aldus,[1] Ian Maidment,[4] Eduwin Pakpahan,[5] Yoon K Loke,[3] Antony Arthur,[1] Nicholas Steel,[3] Clive Ballard,[6] Robert Howard[7] and Chris Fox[3]*

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Background: Sleep disturbance affects around 60% of people living with dementia and can negatively affect their quality of life and that of their carers. Hypnotic Z-drugs (zolpidem, zopiclone and zaleplon) are commonly used to treat insomnia, but their safety and efficacy have not been evaluated for people living with dementia.

Objectives: To estimate the benefits and harms of Z-drugs in people living with dementia with sleep disturbance.

Design: A series of observational cohort studies using existing data from (1) primary care linked to hospital admission data and (2) clinical cohort studies of people living with dementia.

Data sources: Primary care study – Clinical Practice Research Datalink linked to Hospital Episode Statistics and Office for National Statistics mortality data. Clinical cohort studies – the Resource Use and Disease Course in Dementia – Nursing Homes (REDIC) study, National Alzheimer's Coordinating Centre (NACC) clinical data set and the Improving Well-being and Health for People with Dementia (WHELD) in nursing homes randomised controlled trial.

Setting: Primary care study – 371 primary care practices in England. Clinical cohort studies – 47 nursing homes in Norway, 34 Alzheimer's disease centres in the USA and 69 care homes in England.

Participants: Primary care study – NHS England primary care patients diagnosed with dementia and aged > 55 years, with sleep disturbance or prescribed Z-drugs or low-dose tricyclic antidepressants, followed over 2 years. Clinical cohort studies – people living with dementia consenting to participate, followed over 3 years, 12 years and 9 months, for REDIC, NACC and WHELD, respectively.

Interventions: The primary exposure was prescription or use of Z-drugs. Secondary exposures included prescription or use of benzodiazepines, low-dose tricyclic antidepressants and antipsychotics.

Main outcome measures: Falls, fractures, infection, stroke, venous thromboembolism, mortality, cognitive function and quality of life. There were insufficient data to investigate sleep disturbance.

Results: The primary care study and combined clinical cohort studies included 6809 and 18,659 people living with dementia, with 3089 and 914 taking Z-drugs, respectively. New Z-drug use was associated with a greater risk of fractures (hazard ratio 1.40, 95% confidence interval 1.01 to 1.94), with risk increasing with greater cumulative dose ($p = 0.002$). The hazard ratio for Z-drug use and hip fracture was 1.59 (95% confidence interval 1.00 to 2.53) and for mortality was 1.34 (95% confidence interval 1.10 to 1.64). No excess risks of falls, infections, stroke or venous thromboembolism were detected. Z-drug use also did not have an impact on cognition, neuropsychiatric symptoms, disability or quality of life.

Limitations: Primary care study – possible residual confounding because of difficulties in identifying patients with sleep disturbance and by dementia severity. Clinical cohort studies – the small numbers of people living with dementia taking Z-drugs and outcomes not necessarily being measured before Z-drug initiation restricted analyses.

Conclusions: We observed a dose-dependent increase in fracture risk, but no other harms, with Z-drug use in dementia. However, multiple outcomes were examined, increasing the risk of false-positive findings. The mortality association was unlikely to be causal. Further research is needed to confirm the increased fracture risk. Decisions to prescribe Z-drugs may need to consider the risk of fractures, balanced against the impact of improved sleep for people living with dementia and that of their carers. Our findings suggest that when Z-drugs are prescribed, falls prevention strategies may be needed, and that the prescription should be regularly reviewed.

Future work: More research is needed on safe and effective management strategies for sleep disturbance in people living with dementia.

Study registration: This study is registered as European Union electronic Register of Post-Authorisation Studies (EU PAS) 18006.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 1. See the NIHR Journals Library website for further project information.

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Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/hta25010).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

ADC	Alzheimer's disease centre
ARMD	age-related macular degeneration
ATC	Anatomical Therapeutic Chemical
BNF	*British National Formulary*
BMI	body mass index
BZD	benzodiazepine
CDR	Clinical Dementia Rating
CDR-global	Clinical Dementia Rating scored according to standard algorithm
CDR-SOB	Clinical Dementia Rating – Sum of Boxes
CI	confidence interval
CPRD	Clinical Practice Research Datalink
CSDD	Cornell Scale for Depression in Dementia
DDD	defined daily dose
EQ-5D	EuroQol-5 Dimensions
GABA	gamma-aminobutyric acid
GDS	Geriatric Depression Scale
GP	general practitioner
HES	Hospital Episode Statistics
HR	hazard ratio
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICD-10	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision
IMD	Index of Multiple Deprivation
IPTW	inverse probability of treatment weights
IQR	interquartile range
IRR	incidence rate ratio
LRTI	lower respiratory tract infection
MCI	mild cognitive impairment
MD	Doctor of Medicine
MMSE	Mini Mental State Examination
NACC	National Alzheimer's Coordinating Centre
NIHR	National Institute for Health Research
NNH	number needed to harm
NPI	Neuropsychiatric Inventory
NPI-NH	Neuropsychiatric Inventory – Nursing Home
NSAID	non-steroidal anti-inflammatory drug
ONS	Office for National Statistics
OR	odds ratio
PhD	Doctor of Philosophy
PI	principal investigator
PPI	patient and public involvement
PRN	pro re nata
QoL	quality of life
QUALID	Quality of Life in Late-Stage Dementia
RCT	randomised controlled trial
REDIC	Resource Use and Disease Course in Dementia – Nursing Homes
RR	risk ratio
SD	standard deviation
SIB-8	Severe Impairment Battery
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TIA	transient ischaemic attack
UTI	urinary tract infection
VAS	visual analogue scale
WHELD	Improving Well-being and Health for People with Dementia
WHO	World Health Organization
ZED	Z-drug Evaluation in Dementia

Plain English summary

What was the problem?

Poor sleep is common in people living with dementia. It can worsen their own and their carer's quality of life. Sleeping tablets called Z-drugs (zolpidem, zopiclone and zaleplon) are often given to people with dementia.

Some studies suggest that Z-drugs may be harmful, but no studies have looked into the effects of Z-drugs for people with dementia. Good sleep is important, but we need to understand if Z-drugs cause harm.

What did we do?

Using existing medical records, we compared the quality of life, memory and number of falls, infections, strokes, broken bones and deaths for a group of people living with dementia taking a Z-drug, with those for a group not taking any sleep drug.

What did we find?

Z-drug users were no more likely to suffer falls, infection or stroke, but they were more likely to break a bone. We also found that Z-drug users died earlier, but we could not be sure that this was as a result of taking the Z-drug. Using Z-drugs did not appear to affect quality of life or memory.

We talked to carers and health-care practitioners, who told us that decisions about Z-drugs need to balance a range of complicated health and social factors.

What does this mean?

We found that people living with dementia who take Z-drugs are more likely to break a bone or to die sooner than similar people with dementia who are not taking Z-drugs. However, we cannot be certain that these problems are caused by Z-drugs, as many other factors can also lead to broken bones and death.

Further work is needed to clarify the risk of broken bones, but if sleep problems can be managed in other ways then this may be preferable. Patients and family carers should be involved in decisions about Z-drugs, so that they can balance the possible harms against the benefits.

Scientific summary

Background

Dementia is a debilitating disorder affecting memory and cognition. Many neuropsychiatric symptoms are also present, including issues with sleep. Sleep disturbance can encompass insomnia, fragmented sleep, night-time wandering and excessive daytime sleeping, and it affects around 60% of people living with dementia. Sleep is critical for body function, cognitive performance, mood and memory consolidation. This reduction in sleep can have a devastating impact on the quality of life of people living with dementia and their carers, and can hasten care home admission. Pharmacological intervention is commonly used to help initiate and maintain sleep, including the use of hypnotic Z-drugs (zolpidem, zopiclone and zaleplon). These drugs are similar to benzodiazepine hypnotics but were thought to have fewer of the associated side effects, including increased risk of falls, fractures, infections and death, particularly in the older population.

There is now emerging evidence that Z-drug use is also significantly associated with increased risk of falls, fractures, death, infections and cerebrovascular events. Although these drugs are widely prescribed to people living with dementia, there has been little evidence showing their harms and benefits in this population. People living with dementia are already at higher risk of falls and fractures, so understanding any additional harms of Z-drug use is important.

There have also not been studies to address whether or not these drugs are actually effective in people living with dementia (e.g. we do not know if their use improves cognition or quality of life). Improving sleep could be a critical intervention to increase quality of life and improve daily functioning of both patient and carer; however, the risks associated with hypnotic use must be understood to allow a balanced decision-making process when prescribing Z-drugs to people living with dementia.

Objectives

Primary care study

This study was designed to target people living with dementia suffering with sleep disturbance who were prescribed Z-drugs, to estimate the harms associated with first prescription of Z-drugs compared with alternative treatments and no treatment. We also performed a general practitioner validation study to investigate the validity of dementia and sleep disturbance coding in primary care data sets.

Clinical cohort studies

We also investigated what the potential benefits of concurrent use of these medications are, using patient-reported outcomes (including cognition and quality of life) and dementia-based clinical data sets (which were repurposed for analysis in this study).

Design

A series of observational cohort studies using existing data from (1) primary care, linked to hospital admission data and Office for National Statistics data and (2) three clinical cohort studies of people living with dementia.

Data sources

Primary care study

Clinical Practice Research Datalink from English practices, representing 7% of the population linked to Hospital Episode Statistics and Office for National Statistics mortality data.

Clinical cohort studies

1. Resource Use and Disease Course in Dementia – Nursing Homes (REDIC): a longitudinal study of patients admitted to a nursing home who were followed for 3 years and assessed every 6 months, based in Norway.
2. Improving Well-being and Health for People with Dementia (WHELD) in nursing homes: a randomised controlled trial that evaluated an intervention to improve the quality of life of people with dementia living in care homes, based in the UK.
3. National Alzheimer's Coordinating Centre (NACC) clinical data set: a clinical data set based in the USA.

Setting

Primary care study

A total of 371 primary care practices in England.

Clinical cohort studies

Forty-seven nursing homes in Norway, 69 care homes in England and 34 Alzheimer's disease centres in the USA.

Participants

Primary care study

NHS England primary care patients from January 2000 to March 2016, followed for up to 2 years.

Patients were included if they satisfied all the following criteria:

- Their general practice was in England.
- They were diagnosed with dementia, defined as the first of a code for dementia or prescription of a cognitive enhancer (memantine, donepezil, rivastigmine or galantamine), occurring after 1 January 2000.
- They were aged $\geq$ 55 years when diagnosed with dementia.
- There was evidence of a sleep disorder, defined as the first record of a Read code for sleep disorder diagnosis, symptom or referral, or prescription of a Z-drug, low-dose tricyclic antidepressant or melatonin, on or after the dementia diagnosis date and before 31 March 2016 (this first sleep disturbance date defined the 'index date').
- Their records contained at least 3 months of good-quality data before the dementia diagnosis and at least 12 months of data before the index date.

Patients were excluded if there was:

- uncertainty regarding the timing of dementia diagnosis
- a diagnosis of severe mental illness or Down syndrome prior to dementia diagnosis
- a diagnosis of sleep apnoea, sleep-related respiratory failure or alcohol abuse prior to the index date
- a diagnosis of neuropathic pain in the 12 months prior to the index date

- a prescription of sedatives, tricyclic antidepressants or benzodiazepines in the 12 months prior to the index date
- a prescription of multiple sleep medications on the index date
- a prescription of a new antipsychotic, other sedative or other tricyclic antidepressant on the index date
- no linkage possible between Clinical Practice Research Datalink and Hospital Episode Statistics data.

Clinical cohort studies

The REDIC study included people living with dementia or mild cognitive impairment admitted to a nursing home in Norway, with follow-up every 6 months for up to 3 years. The NACC data set included people living with dementia in the USA, followed up annually for up to 12 years. The WHELD trial included people living with dementia admitted to a nursing home in England, with follow-up at 9 months.

Exposures

The primary exposure was prescription or use of Z-drugs. Secondary exposures included prescription or use of benzodiazepines, low-dose tricyclic antidepressants and antipsychotics. Details were extracted for sleep medication prescribed during the follow-up period, including prescription date, dose and duration.

Main outcome measures

In the primary care study, the 16 outcomes assessed were incident (1) fracture in any location; (2) hip fracture; (3) forearm/wrist/hand fracture; (4) fall; (5) mortality; (6) acute bacterial infection; (7) urinary tract infection or acute lower respiratory tract infection; (8) ischaemic stroke/transient ischaemic attack; (9) venous thromboembolism; (10) agitation or psychosis; and additional use of (11) sedatives and other sleep medications; (12) antipsychotics; (13) antidepressants; (14) antibiotics; and health-care utilisation of the number of (15) general practitioner visits and (16) hospital admissions.

The clinical cohort studies examined outcomes of cognition, quality of life, neuropsychiatric symptoms and disability. Specifically, the REDIC study included cognitive outcomes (using the Mini-Mental State Examination, a short eight-item version of the Severe Impairment Battery and the Clinical Dementia Rating – Sum of Boxes); neuropsychiatric symptoms (sleep, anxiety, agitation measured using the Neuropsychiatric Inventory and as part of the Cornell Scale for Depression in Dementia); quality of life (using the Quality of Life in Late-Stage Dementia, using the EuroQol-5 Dimensions and the visual analogue scale); and disability (using the Lawton Physical Self-Maintenance Scale). The NACC data set measured outcomes of cognition (using the Clinical Dementia Rating – Sum of Boxes, Mini Mental State Examination, animal naming and the Trail Making Test delta trail time); neuropsychiatric outcomes (using the Neuropsychiatric Inventory sleep scores, anxiety, agitation and Neuropsychiatric Inventory excluding sleep); the Geriatric Depression Scale (as a proxy of quality of life); and disability (measured using 10 questions on the amount of help needed with each of 10 different activities). The WHELD trial measured neuropsychiatric outcomes (using the Neuropsychiatric Inventory excluding sleep and Neuropsychiatric Inventory sleep scores) and quality of life (using the Quality of Life in Late-Stage Dementia).

Analysis

In the primary care study, Cox proportional hazards regression was used to estimate the association between sleep medication prescription and binary outcomes adjusted for the potential confounders. Negative binomial regression was used to estimate the association between sleep medication and number of general practitioner visits and hospital admissions.

Using the REDIC and NACC data sets, we explored the dynamics and predictors of use of any of three hypnotics (Z-drugs, benzodiazepines or antipsychotics). We used several different analytical approaches to explore associations between use or change in use of hypnotics with changes in cognitive, neuropsychiatric characteristics and quality-of-life outcomes.

In the REDIC study and the NACC data set, linear regression models were used to estimate the association between pattern of hypnotic use and change in each outcome, adjusting for participant age, their baseline cognitive function and visit number. Clustered standard errors were estimated to account for multiple observations per patient. To control for time-varying covariates, inverse probability of treatment weights were also generated, using logistic regression models estimating the probability of treatment at each visit, conditional on previous treatment and previous values of all covariates. Following the method of marginal structural models, these models were used to generate weights reflecting the inverse probability of observed treatment at the current visit, and these weights were applied to simple linear regression models estimating the effect of current hypnotic use on change in outcome measures between waves.

In the WHELD trial, negative binomial regression was used to estimate the association between Z-drug use at baseline and the Quality of Life in Late-Stage Dementia, Neuropsychiatric Inventory excluding sleep and Neuropsychiatric Inventory sleep scores at baseline. Logistic regression was used to estimate the association between baseline Z-drug use and mortality by 9 months' follow-up. Linear regression was used to estimate the mean decline in the Quality of Life in Late-Stage Dementia, Neuropsychiatric Inventory excluding sleep and Neuropsychiatric Inventory sleep scores from baseline to 9 months' follow-up.

Results

A total of 6809 patients were included in the primary care study and 3089 were prescribed Z-drugs. New use of Z-drugs was associated with a greater risk of fractures (hazard ratio 1.40, 95% confidence interval 1.01 to 1.94), with risk increasing with greater cumulative dose ($p = 0.002$). For 42 prescribed defined daily doses onwards, the hazard ratio for a fracture increased to 1.70 (95% confidence interval 1.17 to 2.48). We found evidence of Z-drug use associated with an increased risk of hip fracture (hazard ratio 1.59, 95% confidence interval 1.00 to 2.53) and this rose to a hazard ratio of 2.24 (95% confidence interval 1.29 to 3.91) when cumulatively prescribed ≥ 42 defined daily doses. We also found evidence of Z-drug use associated with mortality (hazard ratio 1.34, 95% confidence interval 1.10 to 1.64), but this association was similar regardless of cumulative exposure to Z-drugs. We also found that people living with dementia who were prescribed Z-drugs were more likely to be initiated on antipsychotics and antidepressants and have more general practitioner and hospital visits. There was no excess risks of falls (hazard ratio 1.05, 95% confidence interval 0.87 to 1.25), acute bacterial infections (hazard ratio 1.09, 95% confidence interval 0.92 to 1.29), ischaemic stroke/transient ischaemic attack (hazard ratio 1.33, 95% confidence interval 0.85 to 2.07), or venous thromboembolism (hazard ratio 1.66, 95% confidence interval 0.69 to 3.98) detected.

In the general practitioner validation study, we found good validity of dementia diagnoses, with 96% of selected patients confirmed to have dementia by their general practitioner. However, we found less validity for sleep disturbance, as only 63% of patients had sleep disturbance confirmed.

In 678 people living with dementia or mild cognitive impairment in the REDIC study, we found that those with better cognitive function were more likely to start using Z-drugs, whereas those with worse cognitive function were more likely to start antipsychotics. Neuropsychiatric symptoms (sleep disturbance, agitation and anxiety) predicted the new use of hypnotics, but there was no evidence that the use of hypnotics causes any significant change in any of the measures that we examined.

In the 17,055 people living with dementia in the NACC data set, we did not observe any significant additional cognitive impairment associated with the use or initiation of Z-drugs, whereas we observed cognitive decline among those taking benzodiazepines or antipsychotics, and those with more severe cognitive function were more likely to be initiated on these drugs. With respect to neuropsychiatric symptoms, there was a significant association between symptom levels and subsequently starting an associated medication, and between starting medications and a concurrent increase in symptoms. As with the REDIC study, there also appears to be no wider impact of hypnotics on quality of life (here as measured by the Geriatric Depression Scale, capturing a patient's own assessment of their mood).

In 926 people living with dementia in the WHELD trial, we observed greater neuropsychiatric symptoms in those taking Z-drugs at baseline (rate ratio 1.24, 95% confidence interval 1.00 to 1.54), but Z-drug use at baseline was not associated with greater improvement in neuropsychiatric symptoms over the following 9 months (mean additional improvement of 0.60 points, 95% confidence interval –3.26 to 4.46 points). We also observed no greater mortality risk in those taking Z-drugs (odds ratio 0.66, 95% confidence interval 0.38 to 1.15).

Limitations

Residual confounding may be possible in the primary care study because of difficulties identifying patients with sleep disturbance and by dementia severity. The limited numbers of people living with dementia taking Z-drugs and not recording medication use and the outcomes continuously restricted analyses in the clinical cohort studies.

Conclusions

Sleep is critical for the health and well-being of an individual; however, in people living with dementia, sleep disturbance is common and often treated with hypnotic medications. To the best of our knowledge, the clinical effectiveness and safety of these drugs have not been assessed in people living with dementia. Using primary care patient data, we observed a dose-dependent increase in fracture and hip fracture risk with Z-drug use in dementia; however, multiple outcomes were examined, increasing the risk of false-positive findings. We also found an association between Z-drug use and mortality, but findings suggest that this is not a causal association. There was also an increase in other prescriptions and higher health-care utilisation in those taking a Z-drug. However, there were no increased risks detected for falls, infections or cerebrovascular events in people living with dementia with sleep disturbance. Further research is needed to confirm the associations observed with Z-drugs and fracture risk, in order to establish whether or not these risks need consideration when prescribing Z-drugs, when balancing the impact of improved sleep of the patient and the carer.

Our clinical studies found no evidence for improved quality of life or cognition with Z-drug use in people living with dementia, but the studies were of insufficient power to address this. Our findings suggest that further research is needed into non-pharmacological alternatives for sleep disturbance in dementia, and into whether or not the prescription of Z-drugs concurrently needs inclusion of risk management strategies to minimise potential fracture risks and adverse health outcomes.

Study registration

This study is registered as European Union electronic Register of Post-Authorisation Studies (EU PAS) 18006.

Funding

Funding for this study was provided by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 1. See the NIHR Journals Library website for further project information.

Chapter 1 Introduction

Scientific background

In the UK, over 800,000 people are living with dementia[1] and it is estimated that global prevalence of dementia will be 65.7 million by 2030.[2] In England and Wales, the number of people living with dementia will increase by 57% between 2016 and 2040, increasing future care demands substantially.[3] Dementia is a debilitating condition predominantly affecting older people, resulting in progressive decline in cognitive and daily function. People living with dementia have higher rates of hospital admission and readmission, worse health outcomes and higher rates of mortality than people without dementia.[4]

Many neuropsychiatric symptoms are also associated with dementia, including aggression, agitation, depression, apathy and sleep disturbance, with nearly all patients developing some neuropsychiatric symptoms during the course of the disease.[5] There are currently no curative treatments for dementia, available treatment options generally manage symptoms.[6] As the disease progresses, disability increases and independence declines, leading to increased use of health and social services. Neuropsychiatric symptoms can cause great distress to family members and carers, contributing hugely to carer burden, stress and poor health,[7] and increases the rate of institutionalisation.[8]

Sleep disturbance in people with dementia

Sleep disturbance can include insomnia, fragmented night-time sleep, night-time wandering and excessive daytime sleeping. The incidence of sleep disturbance in the older population is common, with many older adults reporting insomnia.[9]

Studies show that chronic insomnia predicts poor health, with better health leading to improved sleep patterns,[9] and that disturbed sleep is actually a rarity in older adults who are healthy.[10] Reasons for age-related decline in sleep duration and quality include physical and psychiatric illness.[11,12] Therefore, it is unsurprising that in people living with dementia, sleep disturbance is high, with around 60% of people living with dementia affected.[13,14]

Sleep disturbance in Alzheimer's disease is correlated with further cognitive dysfunction, suggesting that treatment of sleep disturbance could be a strategy to improve cognition in patients.[15] Poor sleep impacts greatly on the quality of life (QoL) of both the patient and their informal carer.[16,17] Furthermore, frequent night-time waking can cause further risks to the individual, including wandering outside (which contributes to significant reductions in carer sleep and increases carer burden),[18–20] and increases the rate of care home admissions for people living with dementia.[21] Sleep disturbance is highly prevalent in people living in care homes, and residents with dementia are reported to have more sleep disturbance then those without dementia.[22] In many cases, this leads to pharmacological interventions being commonly used to manage sleep disturbance in community, hospital and care home settings.[23]

Pharmacological treatment of sleep disturbance: benzodiazepines and Z-drugs

There are several pharmacological treatments available for the management of sleep disturbance in the older population, including hypnotic benzodiazepines (BZDs) and Z-drugs (e.g. zolpidem, zaleplon and zopiclone), hormones (melatonin), antidepressants [typically low-dose tricyclic antidepressant (TCAs)] and antihistamines. The most widely used medications for sleep disturbances in older people are BZDs, low-dose TCAs and Z-drugs.[24]

Low-dose TCAs have sedation effects due to their pharmacological effects of blocking histamine-1 receptors and are used for promoting sleep, but also in pain management and at higher doses for treating depression.[25] BZDs are long acting and act to enhance the effect of gamma-aminobutyric acid (GABA),

an inhibitory neurotransmitter, causing sedation and thus promoting sleep.[26] BZDs are not only given for sleep disturbance, but are also prescribed for a wide range of conditions, including anxiety and agitation.[27] BZDs are associated with a range of adverse side effects, including cognitive impairment, daytime sedation, tolerance, dependence and falls.[28–31] Z-drugs are a newer generation of BZD-like drugs, prescribed exclusively for sleep disturbance. Z-drugs were introduced in the late 1980s, also targeting GABA receptors (similarly to BZDs), to enhance GABA transmission, but with shorter half-lives and claiming to have fewer side effects.[32]

However, there is increasing emerging evidence of adverse effects.[33] The National Institute for Health and Care Excellence *Guidance on the Use of Zalepon, Zolpidem and Zopiclone for the Short-Term Management of Insomnia* recommends that non-pharmacological approaches should be considered first, but that short-acting BZD or Z-drugs can be used for up to 4 weeks, if appropriate.[34] There is no explicit recommendation in these guidelines for use in people living with dementia. Updated guidelines[35] for hypnotics discuss the growing evidence of increased risk of cognitive impairment associated with hypnotic use, but do not specifically address if they are safe for use in people living with dementia. There are no recommendations for pharmacological interventions for sleep disturbance in National Institute for Health and Care Excellence dementia guidelines. A Cochrane systematic review in 2016 concluded that there was a distinct lack of evidence to help guide drug treatment of sleep problems in people living with dementia.[36]

Adverse effects of hypnotic use in the older population

Benzodiazepines and Z-drugs can improve sleep quality, but clinically relevant adverse events are a cause for concern.[37] Risks in people living with dementia have been largely unexplored, but findings from the older population suggest that the consequences of any side effects in people living with dementia could be more severe.

Falls and fractures

It is estimated that 30% of adults aged > 65 years living in the community have at least one fall each year[38] and this is higher for people living with dementia, for whom it is estimated that 50–80% have a fall each year.[39,40] A recent study showed that, over an average of 2.5 years, one-third of people living with dementia had a fall, leading to hospitalisation.[41]

Falls can cause a loss of confidence, potentially resulting in a decline of activity, which can cause further instability and negatively impact QoL.[42] Additionally, fall-related injuries can have a huge impact on subsequent health recovery, leading to a loss of independence, reduced QoL, and are a prominent cause of death and care home admission. Furthermore, fractures, particularly hip fractures, are a significant economic burden to the NHS.[43–46]

There are several risk factors for falls, including medications. BZDs are associated with a 20% increased risk of falls in older people.[47–49] A study of > 9000 patients suffering from Alzheimer's disease and age- and sex-matched controls reported a hazard ratio (HR) of 1.9 [95% confidence interval (CI) 1.0 to 3.6] for BZD prescription and risk of hip fracture,[50] but did not disaggregate Z-drugs. Z-drugs are claimed to have fewer adverse effects, including fewer falls;[51] however, recent studies have shown that Z-drug use is also associated with an increased risk of falls[52,53] and fractures,[54–59] particularly with new Z-drug use.[57,59] A recent systematic review and meta-analysis of 14 studies confirmed these risks, in which Z-drug use was associated with a statistically significant increased risk of fractures, with an odds ratio (OR) of 1.63 (95% CI 1.42 to 1.87) reported.[60] This same study did not, however, find a statistically significant increased risk of falls from Z-drug use. Similarly, a meta-analysis found that Z-drug use was significantly associated with increased risk of hip fracture [risk ratio (RR) 1.90, 95% CI 1.68 to 2.13].[61] These studies have provided key evidence that there is an association between falls and injuries, with hypnotic use particularly in the older population. However, there has been little evidence of the specific effects of hypnotic use in people living with dementia.[62]

Infections

A meta-analysis of randomised controlled trials (RCTs), identified through searches of published sources and US Food and Drug Administration records, found a 1.4- to twofold increased risk of infection in adults exposed to Z-drugs.[63] Some observational studies have similar findings.[64–67] The reason for this finding is unknown, but it has been speculated that hypnotics may impair immune surveillance or the clearing of oral secretions during sleep.[63,68] Infection is more common in people living with dementia than in older persons without dementia, and infection in people living with dementia is a leading cause of mortality, hospitalisation and high cost burden.[4,69]

Mortality

Evidence from studies investigating the association of Z-drug or BZD use with mortality is conflicting,[70–72] with reported associations possibly due to confounding.[73] A US study found that crude mortality rates were higher in people living with dementia taking hypnotics, but the association was not statistically tested.[74] Recently, a study of 31,140 community-dwelling persons with Alzheimer's disease in Finland reported a HR of 1.59 (95% CI 1.35 to 1.88) for mortality after BZD use.[75] The use of Z-drugs, however, was not associated with increased risk of death (HR 1.06, 95% CI 0.83 to 1.35). The study was unable to adjust for sleep disturbance or anxiety.

Cerebrovascular events

People living with dementia have a higher risk of stroke than people without dementia.[76] Recently, BZD use has been associated with a 21% (95% CI 4% to 40%) increased risk of ischaemic, but not haemorrhagic, stroke in 45,050 individuals with Alzheimer's disease in Finland.[77] The study also reported similar stroke risk for Z-drugs. However, the study was unable to adjust for anxiety, sleep disturbance or dementia severity, and only compared individuals with Alzheimer's disease and not specifically those with sleep disturbance. There has also been a report of an increased risk of ischaemic stroke associated with zolpidem.[78]

Other possible harms

Adverse behavioural symptoms have been reported with the use of Z-drugs in the older population, including driving, walking, preparing and eating food, and making telephone calls when asleep.[79] Other symptoms reported include hallucinations, parasomnia and amnesia.[80] Behaviours such as these could be particularly detrimental for people living with dementia, given their vulnerable cognitive state and increased risk of falls.[39]

Potential benefits of hypnotic use

Cognitive functioning

Sleep is crucial for cognitive performance, memory consolidation and mood regulation.[81,82] Sleep loss is associated with reduced cognitive performance.[83,84] Furthermore, observational and experimental studies suggest that poor sleep is a risk factor for cognitive decline and dementia.[85] The underlying mechanisms are unknown, but this suggests that improving sleep quality could be an intervention strategy for dementia, potentially through sedative hypnotics. However, there is evidence that sedative hypnotic use is associated with cognitive decline, with a stronger association observed with long-term exposure,[86–89] although results are conflicting.[90,91] A recent systematic review and meta-analysis suggests that BZD use is associated with increased dementia risk; however, observational studies cannot determine whether the association is a causal effect or due to unmeasured confounders.[92,93] Evidence is emerging that Z-drug use is also associated with dementia risk.[94,95] Despite these findings, there is a lack of studies addressing whether or not sleep drugs are safe for individuals already suffering with significant cognitive decline.[96] It is therefore important to understand if increasing sleep in people living with dementia through pharmacological interventions can maintain cognitive performance.

Quality of life

Sleep disturbance can have a detrimental impact on QoL and health-related quality of life (HRQoL).[97,98] Insomnia has been independently associated with worsened HRQoL to a similar extent as some chronic conditions, including congestive heart failure.[99] Insomnia and sleep disturbance are common in the older population and are associated with decline in QoL.[100] The QoL of carers is also severely reduced when there is a sleep disturbance.[19] Use of hypnotics could be a strategy to increase sleep and thus improve QoL. There have been studies, however, to suggest that use of hypnotics can have a negative impact. In older community-dwelling adults requiring pharmacological treatment for insomnia, hypnotics are also associated with reduced HRQoL.[101] A study of 10,430 older women identified that use of sleeping medications was associated with lower QoL scores in vitality, social functioning, general mental health and bodily pain.[102]

Improving sleep

In dementia, for which sleep disturbance is common, improving sleep could be a valuable intervention strategy to improve cognitive performance. Hypnotics are widely prescribed in this population in an attempt to increase sleep. However, there is increasing evidence that the use of sedating hypnotics in the general population does not improve sleep, cognitive performance or general health, calling into doubt their clinical effectiveness.[103,104]

Study rationale

Sleep disturbance is a common problem in the older population and research suggests that over half of people living with dementia have sleep disturbance.[13] Sleep disturbance affects not only the individual, but also their carer, subsequently leading to a decline in their health and QoL.[17]

Studies suggest that pharmacological therapy for sleep disturbance in the older population can lead to increased rates of falls, fractures and infections. Conversely, untreated sleep disturbance, particularly insomnia, can further impair cognitive function and daily functioning, increase dementia risk and lead to worsening of other health problems.[85,105] The potential harms of BZD and Z-drugs, such as increased rates of falls, fractures and infections, could lead to higher rates of hospitalisation, adding additional financial burden for health systems.[106] Furthermore, adverse events quicken the time to institutionalisation, increasing social care requirements.[8,107]

In 2016, the NHS spent £6M on Z-drugs with 6.53 million prescriptions dispensed in England,[108] and prescriptions of Z-drugs have almost doubled in the UK between 2000 and 2015.[109,110] The proportion of prescribed Z-drugs used specifically by people living with dementia is unknown,[108] but hypnotic prescriptions are common in people living with dementia.[111] Guidance for sleep management in dementia is limited, with little evidence of the safety and efficacy of pharmacological interventions, specifically for people living with dementia.[112] Indeed, a recent review identified a clear absence of RCTs addressing the use and effectiveness of Z-drugs for sleep disturbance in dementia.[36] Identification of safe and effective sleep medications for people living with dementia remains an unsolved challenge.[113]

Together, the personal and societal impact of sleep disturbance for people living with dementia makes it an important priority to quantify the benefits and harms of current pharmacological treatments used in this patient group. This study was specifically designed to evaluate the management of sleep disturbance in people living with dementia, and to provide critical evidence on which clinicians, patients, family members and carers can base care decisions. If significant adverse events are detected when using Z-drugs, this will additionally motivate the development of alternative treatments, both pharmacological and person centred, to improve sleep and outcomes for patients.

Chapter 2 Aims and objectives

Aims

The broad aims of this study were to:

- estimate the harms of using Z-drugs for the management of sleep disturbance in people living with dementia, using UK primary care records (primary care study)
- explore the impact of Z-drugs on cognition and QoL for people living with dementia and their carers, using repurposed clinical study data sets (clinical cohort studies).

Objectives

Primary care study

- To estimate the effects of first prescription of Z-drugs in people living with dementia with sleep disturbance compared with alternative treatments and no treatment. Patient outcomes included:
  - incidence of falls and factures
  - mortality
  - incidence of infection
  - incidence of cerebrovascular events, including ischaemic stroke and venous thromboembolism
  - incidence of behavioural and psychological symptoms
  - additional medication use, including sedatives, antipsychotics, antidepressants and antibiotics
  - health-care utilisation [general practitioner (GP) visits and hospital admissions].
- To validate recorded dementia diagnosis and sleep disturbance codes through a GP questionnaire.

Clinical cohort studies

- To repurpose existing clinical data sets to estimate the impact of concurrent use of Z-drugs on patient- and carer-reported outcomes, including:
  - QoL for patients and carers
  - functional ability
  - cognitive function and sleep disturbance in people with dementia.

Chapter 3 Methods

In this chapter we describe separately the methods for the primary care study and each of the clinical cohort studies.

Study registrations

This work was funded by the National Institute for Health Research (NIHR) under its Health Technology Assessment (HTA) programme (reference 14/221/02) and was conducted in accordance with protocol version 1.2 published on 30 January 2018.

The primary care study protocol is registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance [reference European Union electronic Register of Post-Authorisation Studies (EU PAS) 18006] and approved by the Independent Scientific Advisory Committee for Clinical Practice Research Datalink (CPRD) research (reference ISAC 16_181).

Primary care study

Study design

This was an inception cohort study of people with dementia and sleep disturbance, using data from a UK primary care database. The study design is summarised in *Figure 1*. Briefly, people living with dementia in cohorts prescribed various treatments were followed for the rate of adverse events from their first prescription for sleep disturbance in dementia (index date), until they had a different sleep drug or antipsychotic prescribed, left their general practice, died or at 2 years' follow-up (censor date).

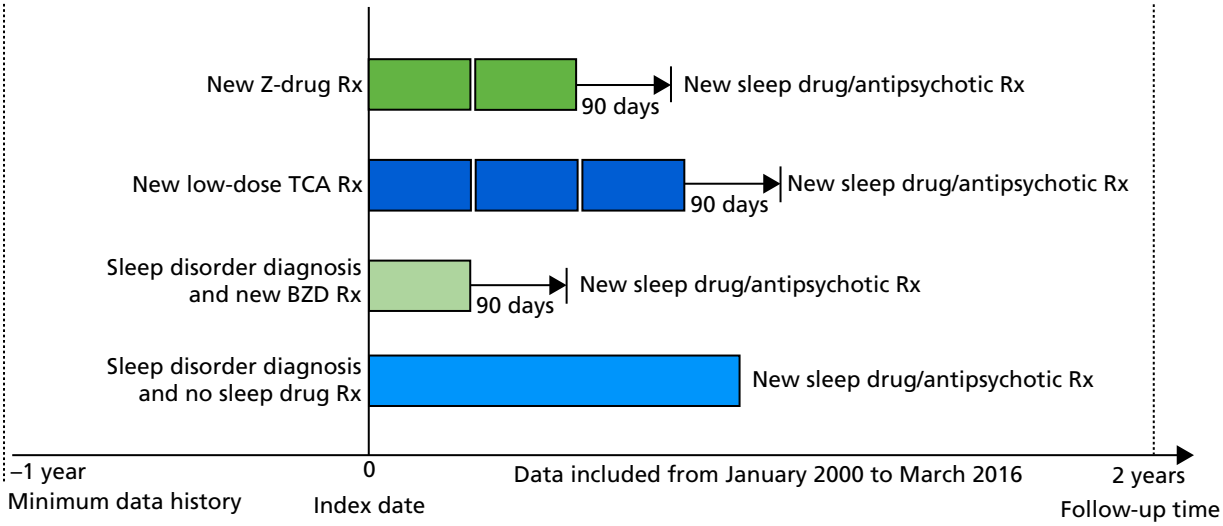

FIGURE 1 Schematic of study design for the primary care cohort study of people living with dementia ($n = 6809$). The four cohorts of patients were followed for at most 2 years or until March 2016. Follow-up for the cohort diagnosed with sleep disturbance but not prescribed sleep medications ended when they received a first sleep medication or antipsychotic prescription. The figure displays theoretical patterns of prescriptions for the cohorts defined by a first Z-drug, BZD or low-dose TCA prescription. Here, follow-up ended if patients had a first sleep medication or antipsychotic prescription, or if it had been > 90 days since their last prescription for a Z-drug, BZD or low-dose TCA, respectively. Rx, prescription.

Setting

This study was undertaken using data extracted from the CPRD. The CPRD includes anonymised diagnosis, referral and prescribing records for > 11.3 million patients from 674 primary care practices across the UK, and is broadly representative of the UK population in terms of age, sex and ethnicity.[114] CPRD data have been widely used for pharmacoepidemiology applications.[115] The diagnosis information recorded in the CPRD is entered as computer-recorded Read codes.[116] Access to 'free text' entered by the GP is not available because of patient anonymity issues.

We used linked data from the CPRD to Hospital Episode Statistics (HES) data version 14, the Office for National Statistics (ONS) mortality data and Index of Multiple Deprivation (IMD) data. HES provides records of all diagnoses made during a hospital admission in England, details on the patient's demographics and place of residence. Diagnoses during the hospital stay are recorded using the *International Statistical Classification of Diseases and Related Health Problems,* Tenth Revision (ICD-10). ONS data include the date and cause of death in England, with cause of death coded according to ICD-10. The IMD is a weighted sum of a number of government indicators, including housing, employment, income, education, living environment and crime levels for each general practice's neighbourhood.[117]

The HES and ONS data sets were linked to CPRD patients by NHS number, date of birth, sex and postcode. The vast majority (92%) of eligible CPRD patients matched to HES, matched on all four characteristics, whereas a further 8% were matched on all but postcode.

Eligibility criteria

Patients were included if they satisfied all the following criteria:

- Their general practice was in England.
- They were diagnosed with dementia, defined as the first of a code for dementia or prescription of a cognitive enhancer (memantine, donepezil, rivastigmine or galantamine), occurring after 1 January 2000. The year 2000 onwards was chosen to exclude historical primary care records when recording was less reliable,[114] and linked mortality and hospital records were only available since 1998.
- They were aged ≥ 55 years when diagnosed with dementia.
- There was evidence of a sleep disorder, defined as the first primary care record for sleep disorder diagnosis, symptom or referral (see *Appendix 1*, *Table 27*, for Read codes), or prescription of a Z-drug, low-dose TCA or melatonin, on or after the dementia diagnosis date and before 31 March 2016 (this first sleep disturbance date defined the 'index date').
- Their records contained at least 3 months of good-quality data before the dementia diagnosis and at least 12 months of data before the index date.

Record of a dementia diagnosis was identified by Read codes in the CPRD (see *Appendix 1*, *Table 26* for Read codes) or ICD-10 codes F00-F03, G30, G31.0 or G31.1 in HES.

Patients were excluded if there was:

- uncertainty regarding the timing of dementia diagnosis, specifically Read codes for a dementia annual review, history of dementia, assessment of psychotic and behavioural symptoms of dementia, or antipsychotic drug therapy for dementia, prior to meeting our dementia diagnosis definition
- diagnosis of severe mental illness or Down syndrome prior to dementia diagnosis (see *Appendix 1*, *Table 28* for Read codes)
- diagnosis of sleep apnoea, sleep-related respiratory failure or alcohol abuse prior to the index date (see *Appendix 1*, *Table 29* for Read codes)
- diagnosis of neuropathic pain in the 12 months prior to the index date (see *Appendix 1*, *Table 30* for Read codes)

- a prescription of sedatives, TCAs or BZDs in the 12 months prior to the index date
- a prescription of multiple sleep medications on the index date
- a prescription of a new antipsychotic, other sedative or other TCA on the index date
- no linkage possible between CPRD and HES data.

Patient selection validation

To validate the accuracy of the coding on which our patient selection was based, a GP questionnaire-based validation study was conducted.[118] In collaboration with CPRD validation services we developed a questionnaire to send to GPs, requesting confirmation of the dementia diagnosis and sleep disturbance status of their patient. The questionnaire was sent to the GPs of 106 randomly selected patients who were still registered with their GP in 2017. The patients selected represented those identified as having sleep disturbance via various Read codes, who were or were not prescribed sleep medications. The questionnaire (see *Report Supplementary Material 1*) asked GPs if the patient had been diagnosed with dementia and the date of diagnosis. It also asked whether or not the patient had a record of a sleep disturbance since being diagnosed with dementia and, if so, on what date. We reported the number of questionnaires returned and the proportions of patients, with their dementia and sleep disturbance confirmed by the GP according to their first medication for sleep disturbance. When the records of dementia or sleep disturbance were not confirmed by GPs, we explored possible causes. We also performed a sensitivity analysis restricted to patients with sleep codes with better validity.

Exposures

The primary exposure of interest was treatment with Z-drugs; secondary exposures were treatment with other medications used for sleep disturbance. The CPRD contains detailed information on all medications prescribed in primary care, including the date of each prescription, drug name, dose, quantity and frequency. We extracted the details of all prescriptions for medications for sleep disturbance for patients in our cohort from their index date up until 31 March 2016.

Sleep disturbance medications were defined according to the World Health Organization (WHO)'s Anatomical Therapeutic Chemical (ATC) Classification System as:

- Z-drugs (N05CF)
- BZDs (N05BA, N05CD)
- melatonin (N05CH)
- low-dose TCA or related (N06AA09, amitriptyline at $\leq$ 25 mg/day; N06AX05 trazodone at $\leq$ 50 mg/day).

Patients were classified according to their prescription class on the index date, or to a 'no prescription for sleep disturbance' group. Patients in the 'no prescription for sleep disturbance' group who then went on to be prescribed any of the medications for sleep disturbance and still met the study eligibility criteria, were then assigned a second index date as the date of this first prescription.

To test for possible dose–response relationships, we determined the cumulative number of prescribed defined daily doses (DDDs) of Z-drugs. A DDD is defined as the assumed average maintenance dose per day for a drug based on its main indication in adults, using the DDD values assigned by the WHO Collaborating Centre for Drug Statistics Methodology (URL: www.whocc.no/atc_ddd_index; accessed 28 November 2019). For each prescription, we multiplied the number of tablets by the dose strength in milligrams and converted this into the number of DDDs, using the values assigned by the WHO. We then summed individual prescriptions to determine the cumulative number of prescribed DDDs, regardless of gaps in use. If the quantity of tablets prescribed was missing, we assumed that one per day (28 tablets/prescription) was prescribed. Prescribing instructions for Z-drugs were also categorised according to whether or not instructions stated pro re nata (PRN) (i.e. use as needed).

The Z-drugs historically prescribed in the UK are zopiclone, zolpidem and zaleplon. The WHO considers the DDD of zopiclone to be 7.5 mg per day, and zolpidem and zaleplon to be 10 mg per day. These values are consistent with the *British National Formulary* (BNF) prescribing guidelines for the recommended daily dose in adults with insomnia.[119,120] For use in the elderly, the BNF recommends using half these daily doses.

Outcome variables

The selected outcome variables were based on adverse effects of medications used to treat sleep disorders identified from previous studies or priorities identified by carers, family members and health-care professionals with direct experience of sleep disturbance in patients.

The 16 outcomes assessed were:

1. incident fracture in any location
2. incident hip fracture
3. incident forearm/wrist/hand fracture
4. incident fall
5. mortality
6. incident acute bacterial infection
7. incident urinary tract infection (UTI) or acute lower respiratory tract infection (LRTI)
8. ischaemic stroke/transient ischaemic attack (TIA)
9. venous thromboembolism
10. incident agitation or psychosis (including symptoms of hallucinations, delusions or aggression)
11. additional use of sedatives and other sleep medications (BNF version 69 subsection 4.1)[120]
12. additional use of antipsychotics (BNF version 69 subsection 4.2.1)[120]
13. additional use of antidepressants (BNF version 69 subsection 4.3)[120]
14. additional use of antibiotics (BNF version 69 subsection 5.1)[120]
15. health-care utilisation of number of GP visits
16. health-care utilisation of number of hospital admissions.

Patients with each outcome were identified using the first mention of a relevant Read code in the CPRD, or ICD-10 code in HES or as a cause of death [Part 1(a) or 1(b)] on the death certificate. See *Appendix 1*, *Tables 31–38*, for a list of the codes to identify the outcomes. Read code lists were drawn, when applicable, from Quality and Outcomes Framework business rules, published studies, keyword searches and UK GP experience within the study team.

Confounding variables

Potentially confounding variables were coded from the CPRD (unless otherwise stated) at the index date. Covariates were selected that are potentially linked to sleep disturbance, dementia or sedative use and at least one of the outcomes, as well as the availability, completeness and reliability of data within CPRD.

Demographic factors

Age, sex, year, care home residence (yes/no/unknown) practice-level IMD quintile, Strategic Health Authority region of England, index date, ethnicity (white/other/unknown).

Health behaviours

Smoking (current smoker, ex-smoker, non-smoker, missing), alcohol use (yes/no/missing), body mass index (BMI) (most recent value in last 5 years categorised as < 18.5, 18.5–24.9, 25–29.9, ≥ 30 kg/m^2 or missing), last systolic blood pressure (most recent value in last 5 years categorised as < 110, 110–119, 120–139, 140–159, ≥ 160 mmHg or missing).

Immunisations in last 12 months

Influenza, pneumonia.

Dementia subtype and proxies for dementia severity

Dementia subtype (Alzheimer's dementia, vascular dementia, mixed/other dementia, unspecified dementia), time since dementia diagnosis, cognitive enhancers in last 90 days, antipsychotic use in last 365 days, history of agitation/psychosis in dementia, end-of-life care (record of palliative care or end-of-life plans having been discussed).

Proxies for sleep disturbance severity

Sleep disturbance diagnosis before dementia diagnosis, previous Z-drug prescription (prior to 12 months before index date), previous BZD prescription (prior to 12 months before index date).

Comorbidities

Osteoporosis, other musculoskeletal conditions, depression, depression symptoms, anxiety, anxiety symptoms, Parkinson's disease, urinary incontinence, age-related macular degeneration (ARMD), glaucoma, cataract, other visual impairment, diabetes, hyperlipidaemia, hypertension, heart attack, heart failure, atrial fibrillation, ischaemic stroke/TIA, angina, venous thromboembolism, osteoarthritis, rheumatoid arthritis, migraine/headache, back/neck pain, cancer and chronic obstructive pulmonary disease.

Medical history in last 12 months

Number of GP visits (0–3, 4–5, 6–8, 9–13 or 14–77), hospital admissions (0, 1 or ≥ 2 using data from HES), a fall, a fracture, LRTI/UTI, dizziness/unsteadiness and faints/syncope.

Concurrent medication use

Any prescription in the last 90 days of selective serotonin reuptake inhibitors (SSRIs), non-SSRIs or TCA antidepressants, other sedatives/hypnotics, antipsychotics, antihistamines, analgesics, antiepileptic drugs, anticoagulants, antiplatelets, cardiac glycosides, diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, lipid-regulating drugs, non-steroidal anti-inflammatory drugs (NSAIDs), bisphosphonates, diabetes drugs, inhaled corticosteroids, calcium/vitamin D and any prescription in the last 30 days for antibiotics.

Data from HES were additionally used to supplement the coding of a history of falls, fractures, LRTI/UTI, ischaemic stroke/TIA, agitation/psychosis, venous thromboembolism, dementia subtype, ethnicity and care home residence.

Statistical methods

We described the characteristics, comorbidities and concurrent medications of the patients in the cohort, using summary statistics according to their initial treatment for sleep disturbance. Using a backwards stepwise procedure retaining a p-value of < 0.15, we developed a multinomial regression model estimating the association between patient characteristics at index date and treatment choice for sleep disturbance.

The primary statistical analysis comprised a series of survival analyses to assess the association between sleep disturbance medication and adverse outcomes. Patients entered the analysis on their index date and were followed until the earliest of:

- the date they left the general practice
- the last general practice data extraction date
- their date of death
- 90 days after their last prescription for their medication for sleep disturbance
- the date of an additional 'medication for sleep disturbance' or other sedative prescription
- the date of a new antipsychotic prescription (for those not prescribed antipsychotics in the year before the index date)
- 2 years after the index date
- 31 March 2016.

Patients were excluded from the analysis of each outcome depending on their history of that outcome. For the fall and fracture outcomes, we excluded patients with a recorded fall or fracture in the 32 days before index date, because of the chance of repeated coding of the same event.[121] For the infections and antibiotics outcomes, we excluded those with an infection or prescription for a medication for infection in the previous 30 days. For the ischaemic stroke/TIA and venous thromboembolism outcomes, we excluded those with a history of these in the previous 30 days. For the analysis of incident agitation/psychosis, we excluded patients who already had a record of agitation or psychosis. For the antidepressant and antipsychotic outcomes, we excluded patients with a prescription for these in the 12 months before the index date.

We used Cox regression models to estimate the HR for the effect of sleep disturbance medication class compared with no prescription on each binary outcome. Sleep medication exposure was modelled as time varying, such that patients at the index date are included for analysis in the 'no treatment' group until initiation of their first treatment, and re-enter the study at time 0 as exposed thereafter to avoid immortal time bias and reduce channelling bias. CIs and *p*-values were calculated using robust standard errors, accounting for the correlation due to some patients appearing twice in the analysis. We checked the proportional hazards assumption using Schoenfeld residuals.[122]

As the number of GP visits and hospital admissions was overdispersed (i.e. the variation was greater than the mean), we used negative binomial regression to calculate incidence rate ratios (IRRs) for the effect of sleep disturbance medication class on number of GP visits and hospital admissions in the 2 years after the index date. For the analysis of GP visits, patients were censored only at the first of either death, leaving the general practice, 31 March 2016 or 2-year follow-up. For the analysis of hospital admissions, patients were censored only at the first of either death, 31 March 2016 or 2-year follow-up.

The primary analysis reported associations relative to no sleep disturbance medication use, and secondary analysis reported associations for the effect of BZDs and low-dose TCAs compared with Z-drug use. Estimates are provided, adjusted for age and sex, and adjusted for all potential confounders listed above and age^2 to allow non-linear effects with age. A quadratic association between age seemed an appropriate parametrisation for most outcomes by examining the association between age in 10 equal categories and the outcome. We performed a sensitivity analysis to this by instead modelling age using fractional polynomials and restricted cubic splines (with five knots). Owing to a small number of events for forearm fractures we adjusted for other eye conditions (ARMD, retinal disorders and glaucoma combined), region combined into only five areas (South, East, Midlands, North and London) and did not adjust for ethnicity or systolic blood pressure.

For statistically significant associations with Z-drugs, interactions between Z-drug and age and sex were tested. In addition, the absolute risks of adverse events and number needed to harm (NNH) were estimated using a standard formula for NNH in time-to-event analysis.[123]

We also carried out analyses of Z-drug exposure according to both time-varying cumulative DDDs (categorised as 0, 1–13, 14–27, 28–41 and $\geq$ 42 DDDs) and by Z-drug dosing instructions on the index date (PRN or not).

Stata® version 14 (StataCorp LP, College Station, TX, USA) was used for data management and statistical analysis. Owing to examining 16 outcomes, the chance of finding a statistically significant association by chance alone had increased. To address this, we used a stricter threshold instead of the traditional *p*-value threshold of 0.05. We used the Benjamini–Hochberg procedure to estimate this critical *p*-value threshold in order to control rate of the false discovery rate (i.e. the proportion of rejected null hypotheses that are incorrect rejections) at < 5%.[124] This is less conservative than the Bonferroni correction,[125] which simply divides the classical *p*-value threshold of 0.05 by the number of hypotheses tested (so our critical threshold would be 0.05/16 = 0.003). To control the false discovery rate, the Benjamini–Hochberg procedure depends on the distribution of *p*-values resulting from the tests, as well as the number of tests performed.

Missing data

We expected incomplete recording of variables, such as smoking and BMI.[126] In the primary analyses, patients with missing covariate data were coded in a missing data category. For covariates with at least 10% of patients with missing data, we summarised the characteristics of those with and without missing data and performed sensitivity analyses, including restricting to patients with and without the missing variable.[127] Finally, we estimated a single imputation model predicting the missing variables using the covariates in *Table 2* and in *Appendix 2*, *Table 39*. For missing BMI data, we additionally used the most recent previously recorded BMI record to impute missing BMI value. We repeated our main analyses using the imputed values.

Sensitivity analyses

We performed various sensitivity analyses of our main analysis. First, based on the findings of the validation study, we repeated our main analysis with an amended definition of sleep disturbance that included diagnoses of sleep disturbance only when not accompanied by a record for a 'satisfactory' sleep pattern. Second, to examine the impact of the source of data used to identify outcomes, we restricted our main analysis to only those outcomes recorded in the CPRD. Third, we compared adverse events in those who initiated Z-drugs compared with those who had recently discontinued them. From the Z-drug cohort we created a further 'discontinued Z-drug' cohort, who after a 90-day period with no Z-drug prescriptions were still eligible for entry to the study. We compared the rates of adverse events in the 'discontinued Z-drug' to the 'Z-drug' cohort.

Protocol changes

The following changes to the analysis plan were made since our protocol:

- We additionally censored patients at their first antipsychotic prescription. Patients initiated on Z-drugs or BZDs were more likely to then start antipsychotics. We additionally censored on first antipsychotic prescription to increase the likelihood that effects observed were due to the Z-drug use and not other sedating medications.
- In our protocol, we aimed to examine incident ischaemic stroke/TIA and incident venous thromboembolism and to exclude anyone with a history of these conditions. However, we found more patients had these histories than expected, so instead we analysed recurrent or incident ischaemic stroke/TIA and venous thromboembolism, and only excluded patients with a history of these in the last 30 days. Findings when excluding all patients with a history of these conditions are available from the authors.
- We made minor changes to the list of potential confounders. We omitted the following prespecified covariates in the analysis due to balance across treatment groups and rare occurrence: phobia, motor neuron disease, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) and multiple sclerosis. We omitted epilepsy and prescription for medications for Parkinson's disease and diabetes, due to collinearity with already included covariates of prescription for antiepileptic medications, diagnosis of Parkinson's disease and diabetes, respectively. Finally, we omitted depression severity and depression duration, as depression diagnosis, depression symptoms, anxiety diagnosis and anxiety symptoms were considered sufficient. Subsequent to the protocol, we have also included the potential confounders of recent prescription for calcium or vitamin D and end-of-life care, based on discussions with our health-care professional advisory panel.
- We omitted a sensitivity analysis using instrumental variables as a result of not finding a sufficiently strong instrument, such that using it would bring greater uncertainty and risk of bias than the main analysis (see *Report Supplementary Material 2* for further details), but instead completed an additional analysis of those patients who discontinued Z-drugs.

A priori power calculation

We performed this a priori power calculation before we had access to HES data and made assumptions as to what the HES data would contain; hence the estimates do not match the final numbers included. There were 32,961 patients with sleep disturbance post dementia diagnosis in the CPRD (July 2017 version).

Of these, 10,554 patients met study eligibility criteria and a further 6117 patients were eligible for HES linkage (HES version 14). Preliminary analysis suggested that on the index date, 2546 patients received a Z-drug, 68 patients received a melatonin, 255 patients received a BZD, 1745 patients received a low-dose TCA antidepressant and 1503 patients received none of the above treatments. We estimated that an additional 50% of dementia patients would be identified via HES (HES set 14 feasibility). Thus, when comparing 3819 Z-drug patients with 2254 patients with no treatment for a common outcome over 2 years (e.g. falls at 36% per year) we can detect a HR of 1.07 with 90% power (two-sample test, $p < 0.05$). For rare outcomes, such as hip fractures at 1.7% per year, we can detect a HR of 1.54 with 90% power.

Clinical cohort studies selection

The second phase of the study utilised data from RCT and cohort studies to estimate how patient-reported outcomes are affected by sleep medication, which cannot be addressed in data extracted from the primary care CPRD database. The following describes the process of identifying clinical cohort studies to examine the outcomes of cognition, neuropsychiatric symptoms, sleep disturbance, disability or QoL of the people living with dementia or their carer, and also the overarching methods applicable to the three clinical cohort studies performed.

Potential studies

We identified several RCT and cohort studies for which data were obtained and descriptive analysis performed to determine their appropriateness for use in this study. Studies were required to have:

- a validated dementia diagnosis for participants
- specific assessment of sleep disturbance for all participants
- at least two assessments per participant, with assessments separated by ≤ 1 year
- at least one key primary outcome (cognition, neuropsychiatric symptoms, sleep disturbance, disability or QoL of the person living with dementia or their carer) included
- systematic assessment of participant medication use, with a documented protocol
- a well-characterised sample, recruited from a defined population with clear inclusion and exclusion criteria
- sufficient sample size (in particular sufficient numbers of participants taking Z-drugs).

Data sources explored, with at least one primary outcome measure, are described in *Table 1*. Those which were not deemed suitable for use in our study were not explored further from initial descriptive analysis. Three data sources that fulfilled the required criteria underwent analysis of patient-reported outcomes. These data sources were:

1. the Resource Use and Disease Course in Dementia – Nursing Homes (REDIC) Norwegian observational longitudinal study
2. the University of Washington's National Alzheimer's Coordinating Centre (NACC) clinical data set
3. the Improving Well-being and Health for People with Dementia (WHELD) RCT based in UK nursing homes.

The REDIC study

Setting

The REDIC study is a longitudinal cohort study of people admitted to nursing homes in Norway. The REDIC study is fully described elsewhere,[133] but in brief the study began in 2012 and recruited 696 patients at admission to one of 47 nursing homes across four Norwegian counties.

TABLE 1 Clinical data sets assessed for repurposing in the ZED study

Database/study name	Study type	Number of participants with dementia	Included in our study
REDIC (nursing homes cohort only)	Observational cohort data to understand socioeconomic consequences of dementia in Norway	678	Yes: good number of participants taking Z-drugs (126 at baseline plus 193 during follow-up)
NACC	Observational cohort data – standardised clinical and neuropathological research data	17,055	Yes: good number of participants taking Z-drugs (373 at baseline plus 72 during follow-up)
WHELD[128]	A RCT of a training intervention in 69 care homes, UK	926	Yes: good number of participants taking Z-drugs (123 at baseline plus 27 at 9 months)
CALM-AD[129]	A pharmacological RCT of donepezil and risperidone over 12 weeks, UK	272	No: low Z-drug exposure
MAGD[130]	A RCT of memantine for agitation in Alzheimer's dementia, UK	153	No: low Z-drug exposure
ADCS[131]	Harmonised data from nine US drug or dietary supplement RCTs, USA	2609	No: low Z-drug exposure
DOMINO-AD (UK)[132]	A RCT of donepezil and memantine for moderate to severe Alzheimer's disease	Aimed to recruit 800	No: low Z-drug exposure

ADCS, The Alzheimer's Disease Cooperative Study; CALM-AD, Trial of a Cholinesterase Inhibitor and Atypical Neuroleptic in the Management of Agitation in Alzheimer's Disease; DOMINO-AD, Donepezil and memantine in moderate to severe Alzheimer's disease – a multicentre RCT; MAGD, Memantine for Agitation in Alzheimer's Dementia: A Randomised Double-Blind Placebo Controlled Trial; NACC, National Alzheimer's Coordinating Centre; REDIC, Resource Use and Disease Course in Dementia – Nursing Home; WHELD, Improving Well-being and Health for People with Dementia; ZED, Z-drug Evaluation in Dementia.

Baseline assessments were made within 1 month of admission to the nursing home and then every 6 months thereafter. Comprehensive REDIC study assessments included questions on sleep disturbance, medication use and measures of cognitive function [recorded by the Mini Mental State Examination (MMSE) and Severe Impairment Battery (SIB-8)], QoL [measured by the Quality of Life in Late-Stage Dementia (QUALID) scale and EuroQol-5 Dimensions (EQ-5D)], neuropsychiatric symptoms [measured using the 12-item Neuropsychiatric Inventory – Nursing Home (NPI-NH)] and depression [measured using the Cornell Scale for Depression in Dementia (CSDD)]. These are described in detail in *Outcome variables*.

We received data from the REDIC study team for assessments up to October 2016, including up to five assessments per participant. Assessments were conducted and supplied in Norwegian, with translation kindly provided by Professor Sverre Burgh, the REDIC study chief investigator.

Participant inclusion and exclusion criteria

Participants were eligible for inclusion in the REDIC study if they had an expected stay in the nursing home for > 4 weeks and were excluded if their life expectancy was < 6 weeks. Participants were included in the Z-drug Evaluation in Dementia (ZED) study if they had a diagnosis of dementia or mild cognitive impairment (MCI) on admission. These diagnoses were made and recorded by the REDIC study team on the first visit after admission to the care home.

Medication exposures

Regularly used medication was recorded at each wave, coded according to WHO ATC code and dose, for up to 18 medications per participant. We coded the presence or absence of three classes of hypnotics at each visit, based on the following codes: Z-drug (Z) – ATC N05CF; BZD – ATC N05BA, N03AE or N05CD; and antipsychotic – ATC N05A.

Outcome variables

Cognitive function

The MMSE and a short eight-item version of the SIB-8 were administered at each wave.[134,135] The MMSE is a well-known and widely used test of cognitive function across several domains, which is scored from 0 to 30 based on the participant successfully answering questions or performing tasks under instruction. The MMSE has good test–retest and inter-rater reliability,[136–139] and performs fairly well in classifying those with dementia and MCI.[140] The SIB-8 aims to measure cognitive function specifically in more advanced Alzheimer's disease and is scored from 0 to 16 based on participants' responses to eight comparatively simple tasks. The SIB-8 has been found to accurately measure progression in advanced Alzheimer's disease and is able to accurately classify dementia stage.[141,142] Both MMSE and SIB-8 are scored with higher scores reflecting better cognitive function.

Dementia severity was measured at each visit by the Clinical Dementia Rating (CDR).[143] In contrast to MMSE and SIB-8, the CDR is scored based on semistructured interview with informants and participants to judge cognitive ability rather than participants' correct responses to specific instructions. The CDR is scored in two different ways. First, measured as a Clinical Dementia Rating scored according to standard algorithm (CDR-global) (0 'no dementia', 0.5 'minimal dementia', 1 'mild', 2 'moderate' and 3 'severe' dementia), according to the standard algorithm. Second, the CDR is often scored as Clinical Dementia Rating – Sum of Boxes (CDR-SOB), which is a simple sum of the level of impairment (scored as 0, 0.5, 1, 2 or 3, as above) in each of the six domains (memory, orientation, judgement and problem-solving, community affairs, home and hobbies, and personal care). CDR-SOB scores range from 0 to 18, with 18 reflecting the maximum level of impairment.[144] The CDR and CDR-SOB have both been reported to have good content and criterion validity, and good inter-rater reliability.[145–147]

Quality of life and disability

Quality of life is measured by the QUALID scale and the EQ-5D.[148,149] QUALID is scored from 11 to 55 based on observations of 11 aspects of patient mood and behaviour in the week before assessment, and is scored such that a lower score is reflective of higher QoL. Although not extensively examined, QUALID has been reported to have good test–retest and inter-rater reliability.[148] The EQ-5D used is the standard assessment of QoL, including a score based on five questions, covering mood and function, as well as a visual analogue scale (VAS) reflecting a single subjective assessment of health scored from 0 to 100. EQ-5D is scored according to country-specific weights; there is no Norwegian-specific EQ-5D scoring and so at the recommendation of the REDIC study investigators the Danish weights are used.[150] These were scored using the EQ-5D command for Stata.[151] The EQ-5D was completed by participants on around one-quarter of occasions, otherwise by care staff. As so few participant scores are recorded, and participant and staff ratings are likely not to be comparable, we used only staff-rated EQ-5D and VAS scores in analysis. Although the EQ-5D is used extensively to measure QoL in Europe and has good validity and reliability, when specifically used in people living with dementia, ceiling effects have been reported and issues in differences across proxy ratings.[152]

Disability is measured by the observer-rated Lawton Physical Self-Maintenance Scale.[153] This scale rates disability from 1 to 5 within six domains of toileting, feeding, dressing, grooming, physical ambulation and bathing, and hence has total scores ranging from 7 to 35. Higher scores reflect greater disability.

Confounders

Sleep disturbance

The NPI-NH was administered at each visit.[154] This includes a screening question on the presence of sleep disturbance, and if this is endorsed then questions on the frequency of sleep disturbance, severity and the extent to which this is occupationally disruptive for the caregiver. The 'occupationally disruptive' question

is analogous to the 'carer distress' question on the original Neuropsychiatric Inventory (NPI). Measures of severity and frequency of sleep disturbance are multiplied together to give an overall sleep disturbance score (scored from 0 to 12). The occupational disturbance question is scored separately on a Likert scale (scored from 0 to 5). If the screening question on sleep disturbance is not endorsed then the occupational disruption and severity questions are all scored as zero.

In addition, three questions on sleep are asked at each visit as part of the CSDD.[155] Informants are asked to evaluate, over the course of the previous week, if the patient has had 'difficulty falling asleep', 'multiple awakenings during sleep' or 'early morning awakening'. Each symptom can be scored as 0 (absent), 1 (mild/moderate) or 2 (severe).

Anxiety and agitation/aggression

As well as sleep disturbance, hypnotics and antipsychotics are used to manage anxiety, or agitated or aggressive behaviour in people with dementia. As with sleep disturbance, these are measured in REDIC study using the NPI-NH [severity, frequency and occupational disruption (distress) associated with anxiety and agitation/aggression] and as items on the CSDD (two questions: severity of agitation and severity of anxiety), each of these scored as for sleep disturbance (see *Sleep disturbance*).

Disability and other covariates

Disability is measured by the observer-rated Lawton Physical Self-Maintenance Scale.[153] Participant age at admission was coded in decades as < 70, 70–79, 80–89 or ≥ 90 years. Educational attainment is coded in terms of years in education as 0–6, 7 (the modal group in this population), 8–12 and ≥ 13 years.

Recoding of outcome measures for analysis

Sleep, anxiety and agitation

The outcome measures of sleep disturbance, QoL, other psychiatric symptoms and cognitive function are also likely to be predictors of future use of medications and so also take the role of time-varying covariates in this analysis.

The distribution of each neuropsychiatric outcome and the Spearman's rank-order correlations between pairs of neuropsychiatric outcomes are shown in *Appendix 3*, *Table 41*. Each outcome, with the exception of anxiety (as measured by CSDD), is endorsed in < 50% of assessments, but there are reasonable numbers of participants who are reported to experience these symptoms in the mild/moderate and severe range. There are very strong correlations between NPI-NH reports of 'total' (severity by frequency) and 'distress' caused by each of sleep, anxiety and agitation, such that the 'total' and 'distress' items can be considered collinear. For this reason, because of the relatively high missing value rate, and for comparison with other studies using NPI-NH that do not use the distress variables, the NPI 'distress' variables are not included in any further analysis.

The diagonal of *Appendix 3*, *Table 41*, shows the auto-correlation of each measure, that is the correlation of each measure with its previous value. These show that although there is some correlation between each measure, there is also considerable fluctuation between waves.

There are some pairwise correlations between other measurements of neuropsychiatric symptoms as expected, in particular when questions aimed to measure similar constructs. A factor analysis of the NPI-NH and CSDD questions on sleep, agitation and anxiety suggested a three-factor solution, with factors corresponding to sleep, agitation and anxiety.

These factor scores are taken forward into future analysis; their distributions are shown in *Appendix 4*, *Figures 26–28*.

Cognitive measures

Appendix 4, *Figures 23–25*, show the trajectories of continuous measures across visits, conditional on the total number of visits completed. The correlation between MMSE and SIB-8 is 0.80, with both measures having a substantial proportion of missing or 0 values (around 20% of occasions in both cases) when participants either did not undertake the assessment or got none of the items correct. These are all coded as 0 for analysis. SIB-8 has a stronger ceiling effect than MMSE, with 10% of SIB-8 scores taking the maximum possible value (16/16) compared with only one maximum possible MMSE score of 30. However, both measures have strong floor effects, caused by a significant proportion of participants being unable to complete any element, hence scoring zero. For this reason, the CDR-SOB was also introduced as a continuous cognitive measure. The CDR is subjectively measured and is successfully completed in 99% of visits, with only 7% of observations taking the maximum or minimum value. CDR-SOB is correlated with MMSE (Spearman's $r = 0.68$) and SIB-8 (Spearman's $r = 0.59$).

Statistical methods

The sample is described with respect to distribution of exposures, outcomes and covariates at baseline, stratified by dementia severity. The number of participants completing each visit is described and the predictors of dropout at subsequent assessment are estimated using logistic regression. The distribution of each outcome with respect to age, visit number, total number of visits completed, CDR and concurrent Z-drug use is then described using data from all pooled together.

Dynamics of medication use

The number of occasions on which Z-drugs, BZDs and antipsychotics are continued, started or stopped between successive visits is shown, along with their co-occurrence. Separate logistic regression models are then estimated to identify predictors of stopping or starting hypnotics between visits. For each hypnotic, stopping is defined as there being no use at the current visit, estimated among those with reported use at the previous visit, whereas starting is defined as use at the current visit estimated among those with no use at the previous visit. Prior values of exposures, outcome measures and all covariates are used as predictors.

Association between hypnotics and outcomes

Three different analyses are used to explore the association between the use of hypnotics (Z-drugs, BZDs and antipsychotics) and each outcome measure. Each addresses a slightly different question and so provides a different perspective on the links.

Change in outcome measure with pattern of medication use between visits

First, each pair of successive visits for each participant is considered as a separate observation, with these recorded as 'previous' and 'current' visits. The change in use of each hypnotic between the visits is coded as 'no use', 'starting use', 'stopping use' or 'continuous use', depending on the medication status at the first (previous) and second (current) visit of the pair. The level of each outcome measure at previous and current visit is also recorded.

The mean average of each outcome is plotted at the previous and current visit, stratified by the change in each hypnotic use between visits. This gives a visual indication of whether stopping, starting or continuing to use each hypnotic affects the change in outcome measures compared with people who do not report the hypnotic at each visit.

A regression model is then used to estimate the association between pattern of hypnotic use and change in each measure, adjusting for participant age, their baseline cognitive function and visit number. One participant can contribute up to four such observations (visits 1 to 2, 2 to 3, 3 to 4 or 4 to 5), and so clustered standard errors for regression coefficients are used to account for multiple observations per participant.

Marginal structural models for time-varying covariates

The models above estimate the rate of change in outcome measures with change in hypnotic use, but do not adjust for prior values of time-varying covariates of cognitive function or neuropsychiatric symptoms, which are shown to predict later use of medication and may also affect change scores.

To control for time-varying covariates, inverse probability of treatment weights (IPTW) are generated using logistic regression models, estimating the probability of treatment at each visit conditional on previous treatment and previous values of all covariates. Following the method of marginal structural models, these models are used to generate weights reflecting the inverse probability of observed treatment at the current visit, and these weights are applied to simple linear regression models estimating the effect of current hypnotic use on change in outcome measures between waves.

Weights calculated in this way aim to balance values of potential confounders across treatment groups, so that any observed differences in current outcome values can be attributed to the treatment of interest. However, some residual differences in prior values remain (as can be seen in *Appendix 3*, *Figures 3–12*, right-hand panels) and so change scores are used as the outcome in regression models as opposed to mean differences at the current assessment. Hence, these IPTW weighted models reflect the effect of hypnotic use on change in outcome measures, accounting for differences in prior treatment and prior of outcome. Standard errors are also corrected for multiple observations per participant.

Fixed-effects regression models

Each of the approaches above considers only pairs of successive observations. So, finally, a longitudinal analysis using fixed-effects models was also conducted. This model compares, for each participant, the values of outcome measures on those occasions when hypnotics are used to the values of outcomes when they are not used. As the comparison is made within participants only, only those participants whose hypnotic use status changes can be included. In addition, this model automatically accounts for any measured or unmeasured covariate, so long as its value does not change within participants. However, it is not possible to correct for time-varying covariates that are also outcome measures. Three fixed-effects models are estimated for each combination of hypnotic and outcome. The first includes all participants, the second includes only those participants with no hypnotic use at all at their baseline visit and the third includes only those participants with minimal or mild dementia (CDR-global score of ≤ 1) at baseline.

The NACC data set

Setting

The NACC data set includes standardised longitudinal patient-level data from Alzheimer's disease centres (ADCs) across the USA. Data include clinical evaluations and records of medication use at the time of assessment. Patients are assessed annually following referral to an ADC, with the first patient entering the study in 2005, and up to 12 assessments recorded for some participants. Full details of the NACC data set and the uniform data set that is collected at each assessment are found in successive publications describing the evolution of the resource over the years and the NACC website (URL: www.alz.washington.edu/; accessed 6 December 2019). The NACC data set is widely used for dementia research and has been previously used for looking at the impact of medication use on different outcomes among people with MCI or dementia.[156] We requested data from every assessment of all participants included in the NACC data set, with an updated data extraction supplied to us in August 2018. This data set included 131,354 visits among 38,249 unique participants.

Participant inclusion and exclusion criteria

For the current analysis, we included only participants with a study diagnosis of dementia at any time and included only their assessments from the point at which they are first recorded as having dementia. Whether or not the participant meets clinical criteria for dementia is recorded at each assessment. This is made according to clinical judgement or by specific criteria, depending on the version of assessment. In analysis we included only those visits when there is a clinical diagnosis of dementia recorded in the

study (NACC coded data set variable 'demented' takes the value of '1'). This reduced data set included 43,286 annual visits among 17,055 unique participants.

Medication exposures

At each annual visit, the medications each participant had used in the 2 weeks before the visit were recorded. Participants were asked to bring medication to the NACC assessment or a detailed list of their medications. When this was not available, it was followed up by a telephone call following the assessment.

Outcome variables

Cognitive measures

At each assessment, a battery of cognitive tests and psychiatric assessments was conducted. Cognitive tests included the MMSE, the Trail Making Test, from which we calculated a delta trail time (trail B time minus trail A time) and an animal naming test, whereby the patient is asked to name as many distinct animals as possible in 60 seconds. MMSE measures general cognitive ability, delta trail time measures attention and task switching, whereas the animal naming test measures language ability and executive function. The Trail Making Test is reported to have good inter-rater reliability.[157]

Further cognitive tests, including the Montreal Cognitive Assessment, were included in later assessments (the third version of the uniform data set), but are not present for the majority of participants and so are not used in the current analysis.

As in the REDIC study, cognitive tests that rely on communication or patients following specific instruction have floor effects or are missing for many severely impaired patients. Hence, the CDR scale was also included: CDR-global was used to stratify patients for descriptive analysis and CDR-SOB was used as an outcome measure. This measure is present for all participants at all visits.

Neuropsychiatric assessments

Neuropsychiatric evaluations included the NPI, although in contrast to the REDIC study only the severity of each NPI item is recorded, as opposed to the 'severity', 'frequency 'and 'distress' variables. Hence, relevant neuropsychiatric symptom, sleep disturbance, anxiety and agitation are assessed at each visit on a 0–3 scale, with 0 corresponding to absence of the symptom, 1 mild, 2 moderate and 3 severe.

To capture the overall burden of neuropsychiatric symptoms, the total NPI score excluding sleep is also included as an outcome measure.

As with cognitive function, more specific items on sleep disturbance are included only in later versions of the NACC data set assessment and so are not included in the current analysis.

Depression

Although there is no available direct measure of QoL, the short form of the Geriatric Depression Scale (GDS) is included in the NACC data set.[158] This includes questions on life satisfaction, helplessness, hopelessness and enjoyment of life that may be considered proxies for a QoL measure, and so GDS is included here as an additional outcome measure. Note, in contrast to many depression measures the short-form GDS does not directly assess sleep disturbance and so should not be directly confounded with measures of sleep. The GDS includes 15 binary items and so is scored from 0 to 15, with higher values indicating more depressive symptoms.

Disability

Disability was measured by 10 questions on the extent to which the participant needed help with each of 10 different activities over the 4 weeks preceding each assessment. The items assessed are writing cheques or paying bills; dealing with taxes or business affairs; shopping; playing games or working on a hobby; heating water, making coffee or turning off the stove; preparing a meal; keeping track of current events; paying attention to a TV show, book or magazine; remembering dates; and travelling.

Each is scored as 0 (no help needed), 1 (does by self but with difficulty), 2 (requires assistance) or 3 (dependent); hence, the total disability scale is scored from 0 to 30. Missing values are omitted at the item level and the total is rescaled if there are fewer than five missing items. If there ≥ 5 out of 10 items missing then the disability score is set as missing.

Statistical methods

Our analysis of the NACC data set follows closely the analysis of the REDIC study data set. First, the characteristics of participants are described stratified by the CDR-global score and the distribution of the total number of study visits with dementia for each participant is shown.

Prevalence and dynamics of medication use

The number of occasions on which each medication of interest at baseline and at subsequent visits is used is described, as well as the dynamics of medication use (number of occasions on which medications are started/stopped between waves). The distribution of each outcome by Z-drug use, CDR, age and change over study visits is shown graphically (see *Figures 23–32*).

Predictors of starting and continuing medication use

Logistic regression models are then estimated for the predictors of medication use at each wave. This model includes the effects of age, sex, visit number, educational attainment of each participant, along with lagged value of cognitive function (measured by MMSE), NPI sleep, NPI excluding sleep and GDS. As lagged values of covariates are included, only data from the second visit onwards are included in these models. Separate models are estimated for continuing medication use (report of drug among those reporting use at the previous wave) and starting use (reporting of drug among those not reporting use at the previous wave).

Effect of medication use on outcomes

First, the changes in outcome measures between waves are then described and plotted, stratified by whether each of Z-drugs, BZDs or antipsychotics are started, stopped, continue or are absent altogether between waves. These associations between change in outcome measures and change in medication use status are estimated using a linear regression model, adjusting for age group, baseline cognitive function and visit number, with clustered standard errors to account for multiple records per person.

Second, a marginal structural model is used to estimate the effect of each medication, with IPTW used to correct for differences in prior values of outcome measures and exposures between exposed and unexposed groups.

Finally, fixed-effects longitudinal models are estimated, modelling the association between each medication use and each outcome, hence automatically accounting for any between-patient effect (thereby automatically controlling for both measured and unmeasured fixed covariates), although not accounting for time-varying covariates. The following specific models were estimated, mapping those estimated using the REDIC data set:

- model 1: effect of each drug on each outcome, among all participants with no adjustment for time varying covariates
- model 2: as model 1 but including only participants with no hypnotic use at baseline
- model 3: as model 1 but including only participants with a CDR-global score of < 2 (i.e. include only those with mild or minimal dementia at baseline).

Software

Clustered linear models and weighted linear models are estimated using the 'survey' package and fixed-effects linear models are estimated using the 'plm' package version 1.6-6 (linear models for panel data) for R statistical software version 3.5.0 (The R Foundation for Statistical Computing, Vienna, Austria). The data set was cleaned and coded using R as well as Stata. All other analysis was conducted using R, with the 'stargazer', 'dplyr' and 'ggplot2' packages for data manipulation, managing outputs and plotting, respectively.

The WHELD trial

Setting

This study was undertaken using anonymised data from the WHELD cluster randomised controlled two-arm trial, covering 69 care homes in England.[128,159] The RCT was carried out between January 2013 and September 2015, with a primary aim to determine whether or not an optimised staff training intervention improved the QoL and mental health of people with dementia living in nursing homes.

Participant inclusion and exclusion criteria

Care homes and their residents were eligible for inclusion in the WHELD RCT if the:

- care home has > 60% of residents with dementia
- care home was not receiving special support from their local authority
- care home met the five CQC care home quality standard checks
- resident had a diagnosis of dementia or had a score of ≥ 1 on the CDR.

Care homes and their residents were excluded from the WHELD RCT if:

- the care home had insufficient staffing resources or anticipated major change during the study period
- the care home was involved in other research or undergoing a systematic programme of service improvement
- consent or advice from a consultee could not be obtained for the resident.

A total of 971 participants met the inclusion criteria, with 504 participants randomised to receive treatment as usual and 467 to receive the WHELD intervention between January 2013 and April 2014. Follow-up assessments were available for 553 participants 9 months later and non-completion was mainly due to mortality.

Participants were not included in the ZED analysis if it was not possible to record their medication usage at baseline or had a reported diagnosis of severe mental illness (schizophrenia or bipolar disorder) at any assessment.

Medication exposures

Antipsychotic and other psychotropic drugs taken at each assessment were classified according to the BNF.[120] Drugs were coded as non-BZD hypnotics, BZDs, antidepressants, carbamazapine, sodium valproate, other anticonvulsants, memantine, cholinesterase inhibitors, barbiturates, clomethiazole, nuspirone and others.

Outcome variables

The following outcomes were assessed prior to randomisation and after 9 months of the intervention.

Patient quality of life

Measured using the QUALID. Lower scores indicate better QoL.

Neuropsychiatric symptoms (excluding sleep)

The NPI-NH was used to assess neuropsychiatric symptoms in people with dementia.[154] The NPI-NH assesses a broad range of symptoms, including delusions, hallucinations, agitation, depression/dysphoria, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability, aberrant motor behaviours, night-time behaviours and appetite/eating change. Severity scores (1–3) multiplied by frequency score (1–4) were given for each item, resulting in a score ranging from 0 to 12, with a higher score indicating more severe symptoms. The question on sleep disturbance was excluded to give a total maximum score of 132.

Sleep disturbance

The NPI night-time behaviours question 'Does the patient awaken you during the night, rise too early in the morning, or take excessive naps during the day?' was used to assess sleep disturbance in people living with dementia.

Confounding variables

The following confounding variables were considered at baseline: age, sex, ethnicity (white or not), marital status (single/widowed, married/long-term partner, divorced/separated), CDR (mild, moderate, severe), sleep disturbance (a NPI-NH sleep score > 0), Abbey Pain Scale score (0–2 = none, 3–7 = mild, ≥ 8 = moderate/severe), comorbidity (depression, anxiety, respiratory illness, gastrointestinal illness, cardiovascular condition, endocrine illness, musculoskeletal disorder and nervous system illness) and co-medication use (BZD, meprobamate/buspirone, clomethiazole, antidepressant, antipsychotic cholinesterase inhibitor and memantine).

Statistical methods

Care home participant characteristics were described for those who were and were not taking Z-drugs at baseline. Negative binomial regression was used to estimate IRRs for the association between Z-drug use at baseline and QUALID, NPI-NH excluding sleep and NPI-NH sleep scores at baseline. Logistic regression was used to estimate ORs for the association between baseline Z-drug use and mortality by 9-month follow-up. Linear regression models were used to estimate the mean decline in QUALID, NPI-NH excluding sleep and NPI-NH sleep scores from baseline to 9-month follow-up for Z-drug use compared with no use at baseline, as well as for continuing, starting or stopping Z-drug use between baseline and 9-month follow-up compared with no use. All associations are presented both unadjusted and adjusted for the covariates listed above. For the analysis comparing changes of Z-drug use across the 9-month follow-up, changes in the use of antidepressants, memantine, antipsychotics and BZDs were also adjusted for.

Chapter 4 Study management

Patient and public involvement

Patient and public involvement (PPI) was an important part of the ZED study. In this section, we detail the different ways in which PPI members contributed to the development and progression of the study during its course.

There was early engagement of PPI participants during the protocol design process to highlight important outcomes to investigate, based on their personal experiences of dementia and sleep disturbance, including its management. PPI members were recruited from Inspire, a PPI group based at the Norfolk and Suffolk NHS Foundation Trust. PPI members included older people with an interest and experience relevant to dementia research. A PPI meeting attended by six panel members was conducted in June 2016 during the initial study stages, from which two members were invited to be part of the annual Study Steering Group meetings and thus allow the continued contribution of PPI members during the study. Feedback from this initial meeting influenced protocol design of the CPRD work package. For example, PPI members helped prioritise the outcomes to be investigated. Their main priority was falls, due to the risk of fractures. They were also keen to see comparisons of Z-drugs with other, alternative treatments. They were keen to see the effect of using Z-drugs at different doses, for different durations and when using them sparingly, rather than every day. There were three Study Steering Group meetings during the study, of which one had a member of PPI present. Additionally, an update was communicated by e-mail in 2017 to keep all PPI participants involved in the study as it progressed. A second and final meeting took place in June 2018 to discuss the results of the study and interpretations from a PPI perspective. We also asked our PPI team for their advice on dissemination activities and publication strategies.

Health-care professional advisory panel

Hypnotic medication is widely prescribed in different health-care settings; in order to inform on hypnotic prescribing experience across different health services we had a second public group, a health-care professional advisory panel consisting of a mental health pharmacist, a clinical doctor specialising in older person and dementia care, a community nurse and a GP. An initial meeting took place in June 2016, during protocol development stages, when we sought advice on sleep disturbance coding in primary care and personal experiences of prescribing hypnotics in people living with dementia. A second meeting took place in April 2018 to discuss the final results of the study, when we sought advice on interpretations of the data and on which health-care professionals to target during our dissemination activities.

Patient and public involvement and health-care professional panel reflections

Although our study was based on secondary data analysis, we found the PPI and health-care professional input vital. Listening to the various different experiences described by carers in the PPI panel whose family member had sleep disturbance and the various approaches used in different settings to manage sleep disturbance described by the health-care professional panel helped us to focus our analyses and interpret the findings.

The PPI members highlighted the importance of the care setting and who the primary carers were in the management of sleep disturbance and the outcomes. This encouraged us to code, as best we could, whether or not the person living with dementia was in a care home.

The PPI members discussed comorbidities and the impact if, for example, the person living with dementia, also had a UTI. Hence, we were careful to consider this and include as a potential confounder in our analyses. The meetings also helped us refine our coding lists for the CPRD, especially regarding different terms for 'sleep disturbance'.

Although the outcomes we could examine were limited by the NIHR commissioned call, it was still valuable for PPI members to discuss the relative importance of these and see if any others needed to be added. Owing to time constraints, personnel changes and changes within the PPI group, we had limited ability for the PPI members to contribute to the statistical analysis and interpret the results as they became available. However, the dissemination meeting was very important to help understand the importance of downplaying the association between Z-drugs and mortality, emphasising the needs of the carer and the person living with dementia together, and of clearly communicating absolute risks and risk differences alongside the HRs of outcomes when reporting the findings.

Study management

A Study Steering Group met regularly throughout the study to provide oversight and expertise. Study Steering Group meetings were organised throughout the study; PPI representatives were also invited to take part in these meetings to encourage a public perspective on study plans and progression.

Ethics approval

The primary care study was approved by the Independent Scientific Advisory Committee for CPRD for CPRD research (reference 16_181). No further ethics approval was required for the analysis of the data. The CPRD group has obtained ethics approval from a Multicentre Research Ethics Committee for all purely observational research using CPRD data.

The Regional Ethics Committee for Medical Research in South-Eastern Norway approved the REDIC study (reference 2011/1738a). The patient's capacity to consent to participation in the study was considered by the nursing home staff, including the physician. Written consent for participation was obtained from all participants with the capacity to consent. For participants lacking the capacity to consent, their next of kin gave consent on behalf of the patients. The next of kin gave written consent for their own participation in the study, as they provided information about themselves.

All participants or their legally authorised representatives signed informed consent prior to participation in the NACC study. The institutional review board overseeing each ADC approved local procedures.

Ethics approval for the WHELD RCT was obtained from the South-Central Oxford Research Ethics Committee C (reference 11/SC0066). The trial is registered as a clinical trial (ISRCTN40313497). Consent for nursing home involvement was obtained from the management of the homes. If residents lacked capacity, informed consent was obtained through the involvement of a nominated or personal consultee who represented the residents' interests and wishes in accordance with the Mental Capacity Act.[160]

Funding

The NIHR HTA programme (reference 14/221/02) funded the Z-drugs in dementia (ZED) study.

Sponsorship

The University of East Anglia was the study sponsor.

Chapter 5 Primary care study results

Study cohort selection

The CPRD database contained data from 17.1 million patients in the UK in July 2017, of whom 8.3 million were from English practices with linkage to HES data. Of these, 15,842 patients were diagnosed with dementia at age ≥ 55 years between 1 January 2000 and 31 March 2016, and met our definition of having a sleep disturbance on or after the dementia diagnosis (*Figure 2*). We excluded 8972 patients from analysis who did not meet our inclusion criteria, as further described in *Figure 2*. As there was an insufficient number of patients ($n = 61$) first prescribed melatonin to analyse the outcomes for this drug, the patients prescribed melatonin were excluded, leaving 6809 patients in the study cohort for analysis. Of the included patients, 2952 patients were prescribed a Z-drug on the index date, 1898 patients were prescribed a low-dose TCA, 308 patients were prescribed a BZD and 1651 patients were not prescribed sedative medication.

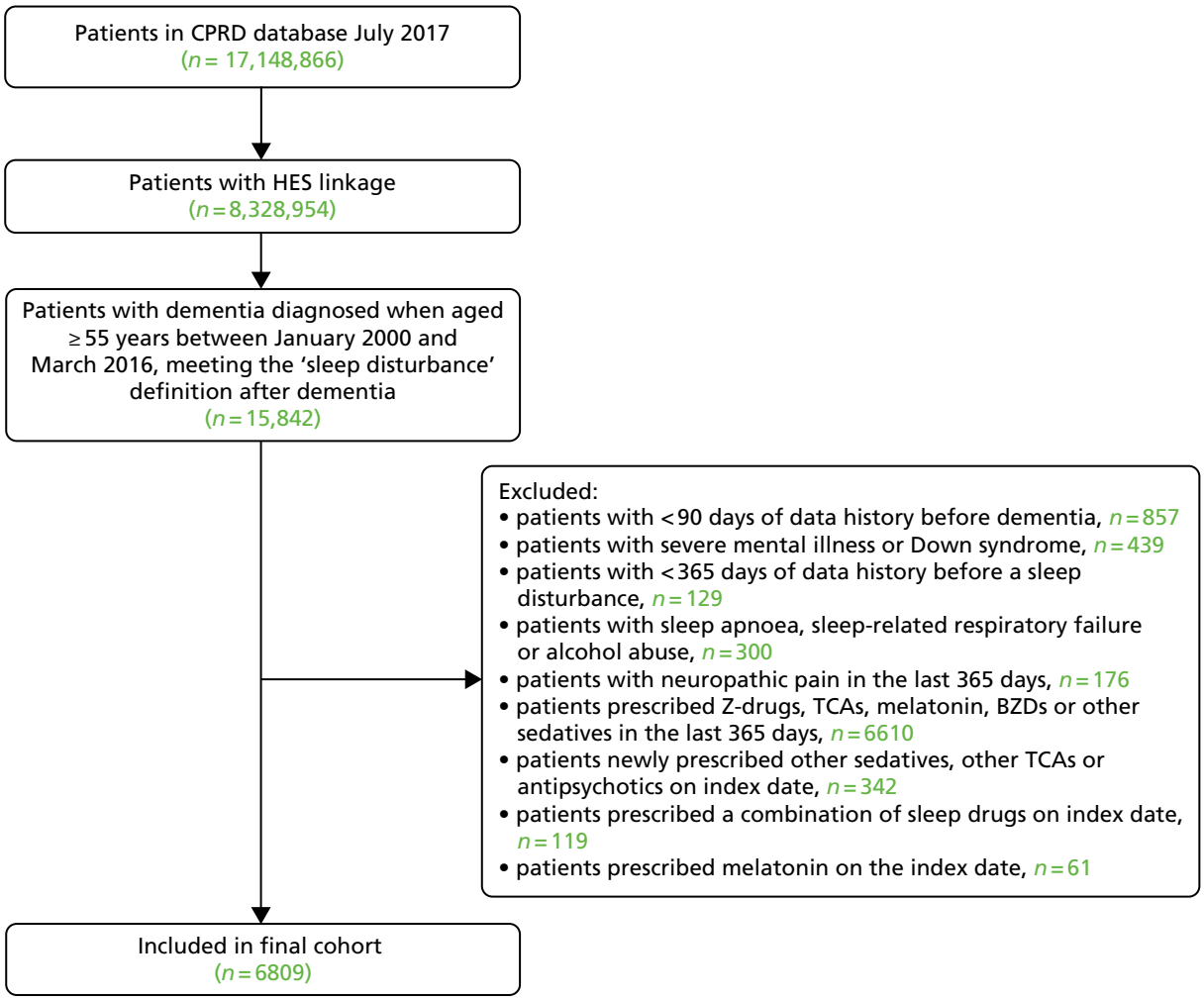

FIGURE 2 Selection of patients for the primary care study cohort.

Patient characteristics

The mean age of included patients at index date was 83 [standard deviation (SD) 7.5] years and 4127 (61%) of the patients were women. General practices were located across England and patients had been registered with their general practice for a median of 20 [interquartile range (IQR) 12–33] years before their first recorded sleep disturbance in dementia. As per the study design, 100% of patients in the BZD and 'no sleep medication' cohorts had a diagnosis of sleep disturbance on their index date. A total of 572 (19%) and 73 (4%) of the Z-drug and low-dose TCA cohorts had a diagnosis of sleep disturbance on the day of their index date. Further patient characteristics, comorbidities and concomitant medications can be found in *Table 2* and in *Appendix 2*, *Table 39*.

TABLE 2 Patient demographics and health behaviours by first sleep disturbance treatment

Characteristic	First sleep disturbance treatment			
	Z-drug (*N* = 2952)	Low-dose TCA (*N* = 1898)	BZD (*N* = 308)	No drug (*N* = 1651)
Female, *n* (%)	1723 (58)	1193 (63)	175 (57)	1036 (63)
Age (years), mean (SD)	83.0 (7.7)	82.3 (7.3)	82.9 (7.7)	83.2 (7.1)
White ethnicity, *n* (%)	2725 (92)	1782 (94)	265 (86)	1503 (91)
Ethnicity missing	165 (6)	86 (5)	37 (12)	111 (7)
Care home residence, *n* (%)	694 (24)	409 (22)	69 (22)	393 (24)
Residence missing	1059 (36)	727 (38)	113 (37)	439 (27)
Index year, median (IQR)	2009 (2006–12)	2010 (2007–13)	2007 (2004–10)	2008 (2005–12)
General practice region (England), *n* (%)				
North	692 (23)	517 (27)	68 (22)	442 (27)
Midlands	463 (16)	221 (12)	39 (13)	330 (20)
East	326 (11)	179 (9)	49 (16)	247 (15)
South	1184 (40)	847 (45)	134 (44)	503 (30)
London	287 (10)	134 (7)	18 (6)	129 (8)
General practice area IMD quintile, mean (SD)	3.2 (1.4)	3.1 (1.4)	3.1 (1.4)	3.5 (1.4)
Health behaviours				
Smoking status, *n* (%)				
Non-smoker	1947 (66)	1233 (65)	203 (66)	1101 (67)
Ex-smoker	635 (22)	472 (25)	58 (19)	374 (23)
Current smoker	257 (9)	147 (8)	31 (10)	129 (8)
Missing	113 (4)	46 (2)	16 (5)	47 (3)
Alcohol user, *n* (%)	605 (20)	428 (23)	54 (18)	440 (27)
BMI (kg/m^2), mean (SD)	24.7 (4.8)	25.0 (4.8)	24.8 (4.7)	24.5 (4.6)
BMI missing, *n* (%)	932 (32)	511 (27)	111 (36)	435 (26)
Systolic blood pressure (mmHg), mean (SD)	134.0 (19.2)	134.4 (17.9)	134.9 (20.6)	133.8 (19.1)
Blood pressure missing, *n* (%)	81 (3)	44 (2)	18 (6)	26 (2)

Examination of predictors of first sleep disturbance medication revealed small differences between the groups (see *Appendix 2, Table 40*). Patients had a greater chance of being prescribed Z-drugs if they were a man, had a history of fractures or hospitalisation, or had recent antipsychotic or analgesic use. Those prescribed BZDs were more likely to be men, have osteoporosis, have a history of agitation or psychosis, and have recent antiepileptic and NSAID use. Patients prescribed low-dose TCA had fewer falls and were more likely to have neuropathic, back and/or neck pain or headaches, and recent NSAIDs, antiplatelets and analgesic use, but less SSRI or other antidepressant use. Those not prescribed sleep drugs were more likely to be from a deprived neighbourhood, have a falls history, have more frequent GP visits and have a history of urinary incontinence and of insomnia before dementia, but not to have a history of prior BZD or Z-drug use. Low-dose TCAs and Z-drugs were more likely to be prescribed in recent years (2010), whereas BZDs were more likely to be prescribed in earlier years (2007).

Validation study

A total of 56 (53%) GPs completed our validation questionnaire. The GPs confirmed a diagnosis of dementia for 54 (96%) of the patients (*Table 3*). The dementia diagnosis date recorded by the GP was very similar to the date we recorded (74% were within 1 month). Sleep disturbance was confirmed for fewer patients, with 35 (63%) patients confirming sleep disturbance.

This varied by which drug cohort the patient was in, such that 82%, 60% and 42% of the patients in the Z-drug, low-dose TCA and 'no sleep drug' cohort were identified by the GP as having sleep disturbance, respectively.

Further inspection of the patient records revealed that additional information recorded when certain insomnia and sleep disturbance Read codes were entered resulted in the GP software providing a 'pop-up screen' asking for the GP to record the patients' 'sleep pattern'. For 11 of the 13 patients (85%) with a sleep disturbance code and for whom the GP did not report a sleep disturbance, the record of sleep disturbance also occurred alongside a record of 'satisfactory' 'sleep pattern' on the pop-up screen (*Table 4*).

TABLE 3 Overall results of the GP validation study, by sleep drug at index date

	Sleep disturbance treatment							
	Z-drug (*N* = 46)		Low-dose TCA (*N* = 32)		No drug (*N* = 28)		Total (*N* = 106)	
Questionnaire result	*n*	%	*n*	%	*n*	%	*n*	%
Valid questionnaires returned	22	48	15	47	19	68	56	53
Dementia verified by GP	22	100	14	93	18	95	54	96
Sleep disturbance verified by GP	18	82	9	60	8	42	35	63

TABLE 4 Sleep disturbance validation results for those with sleep disturbance diagnosis on index date

'Satisfactory' sleep pattern coded on index date	Number of patients	Number of patients (%) with sleep disturbance confirmed
Yes	17	6 (35)
No	12	10 (83)
Total	29	16 (55)

Owing to the validation study findings, we performed a sensitivity analysis with an amended definition of sleep disturbance that excludes Read codes accompanied by a record of 'satisfactory sleep pattern' on the GP pop-up screen. We also advise caution interpreting any risks estimated with low-dose TCAs, as we could not confirm that sleep disturbance was the indication for many of these prescriptions, and people living with dementia with chronic pain may have different risks of the adverse outcomes than those with sleep disturbance.

Patient follow-up

A total of 137, 44 and 135 patients from the 'no sleep disturbance treatment' group subsequently met the criteria for the Z-drug, low-dose TCA and BZD groups, respectively. Hence, each of these patients occur in the analysis twice.

Patients were followed for a median of 3.2 (IQR 2.3–9.1) months. The main reason for censoring was patients having no further Z-drug, BZD, or low-dose TCA prescriptions for 90 days, from each cohort, respectively (*Table 5*). The second most common reason for censoring was because of a new sedating medication being prescribed. This resulted in a median follow-up for each cohort of 3.0 (IQR 1.8–5.3), 3.2 (IQR 3.0–8.7), 3.0 (IQR 2.0–5.0) and 8.9 (IQR 2.8–23.9) months for the Z-drug, low-dose TCA, BZD and no sleep disturbance treatments groups, respectively.

For the sensitivity analysis, of the 3089 patients prescribed Z-drugs, 1274 of them stopped receiving prescriptions and met the inclusion criteria to be included in a 'discontinued Z-drugs' cohort. Their median follow-up was 9.1 (IQR 3.0–22.1) months and the most common reason for censoring was being prescribed a new sedating medication. A total of only 280 (22%) were censored as a result of receiving another Z-drug prescription.

TABLE 5 Reasons for ceasing follow-up according to sleep drug at index date

	Sleep disturbance treatment at index date[a]									
	Z-drug (*N* = 3089)		Low-dose TCA (*N* = 1942)		BZD (*N* = 443)		No drug (*N* = 1651)		Discontinued Z-drug (*N* = 1274)	
Censoring reason	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Death	351	11	192	10	64	14	261	16	179	14
Transferred out	311	10	165	8	33	7	269	16	209	16
Last practice data extraction	69	2	85	4	7	2	106	6	95	7
New sedative drug	906	29	396	20	119	27	527	32	510	40
Z-drug	0	0	70	4	40	9	149	9	280	22
Low-dose TCA	119	4	0	0	17	4	46	3	30	2
BZD	440	14	167	9	0	0	161	10	115	9
Melatonin	11	0	< 5	0	< 5	0	5	0	< 5	0
Other sedative	35	1	17	1	6	1	24	1	15	1
Antipsychotic	305	10	142	7	55	12	149	9	69	5
No prescription for 90 days	1306	42	921	47	193	44	0	0	0	0
End of study (2 years)	123	4	143	7	23	5	411	25	213	17
End of study (31 March 2016)	23	1	40	2	< 5	1	77	5	68	5

a Includes 137, 44 and 135 patients twice who occur in the 'no drug' cohort first and then later in the Z-drug, low-dose TCA and BZD cohorts, respectively. The 1274 patients in the 'discontinued Z-drug' cohort also occur in the 'Z-drug' cohort.

First prescription for sleep disturbance

The first sleep disturbance prescriptions issued to the cohort are described in *Table 6*. Of the 3089 patients receiving Z-drugs, the majority (95%) were prescribed zopiclone. The most common daily dose prescribed of zopiclone was 3.75 mg (80%). The most common low-dose TCA prescribed was amitriptyline (57%) and the most common BZD prescribed was temazepam (64%).

During the median 3.0 (IQR 1.8–5.3) months' follow-up for the cohort initiated on Z-drugs, 1484 (48%), 429 (14%), 212 (7%) and 964 (31%) go on to receive none, one, two and three or more further Z-drug prescriptions.

Fractures, falls and mortality

A total of 368 patients experienced a fracture during follow-up, with around half of these being hip fractures. A total of 1078 patients reported a fall to their GP or were admitted to hospital with a recorded fall. Overall, 883 patients died during follow-up.

Table 7 displays the incidence rates and HRs for fractures, falls and mortality for the different sleep disturbance treatments, relative to no prescription for sleep disturbance, adjusted for age and sex, and adjusted for all potential confounders. Generally, there was little difference between the full adjustment for confounders and adjustment for just age and sex. The incidence of fractures in patients receiving Z-drugs was 11.3 per 100 person-years. In patients receiving BZDs, low-dose TCA or no prescriptions for sleep disturbance, the incidence of fractures was 12.0, 10.2 and 7.3 per 100 person-years, respectively. After adjustment for potential confounders, prescription of Z-drugs was associated with a greater incidence of fractures, with a HR of 1.40 (95% CI 1.01 to 1.94).

TABLE 6 First sleep disturbance medication prescription

First prescription	Number of patients	Per cent within class
Z-drug		
Zaleplon	12	0.4
Zolpidem	138	4.5
Zopiclone	2939	95.1
Low-dose TCA		
Amitriptyline	1116	57.5
Trazodone	826	42.5
BZD		
Diazepam	54	12.2
Lorazepam	50	11.3
Lormetazepam	13	2.9
Midazolam	14	3.2
Nitrazepam	21	4.7
Oxazepam	6	1.4
Temazepam	285	64.3

TABLE 7 Adjusted HRs for fractures, falls and mortality, by sleep disturbance medication

Outcome and sleep medication	Patients (*n*)		Incidence/ 100 PYs	Age, sex adjusted		Adjusted[a]	
	Exposed	With outcome		HR	95% CI	HR	95% CI
Fracture							
No sleep drug	1636	108	7.3	1.00		1.00	
Low-dose TCA	1913	105	10.2	1.29	0.98 to 1.70	1.12	0.80 to 1.58
BZD	433	20	12.0	1.41	0.87 to 2.29	1.34	0.69 to 2.61
Z-drug	2997	135	11.3	1.39	1.06 to 1.82	1.40	1.01 to 1.94
Hip fracture							
No sleep drug	1636	47	3.1	1.00		1.00	
Low-dose TCA	1913	56	5.3	1.59	1.06 to 2.38	1.53	0.95 to 2.48
BZD	433	12	7.1	2.01	1.03 to 3.93	2.07	0.72 to 5.97
Z-drug	2997	66	5.4	1.53	1.02 to 2.27	1.59	1.00 to 2.53
Forearm/wrist/hand fracture							
No sleep drug	1636	18	1.2	1.00		1.00	
Low-dose TCA	1913	16	1.5	1.11	0.57 to 2.19	0.99	0.35 to 2.79
BZD	433	< 5	N/A	N/A			
Z-drug	2997	27	2.2	1.83	0.94 to 3.56	1.29	0.53 to 3.15
Fall							
No sleep drug	1506	328	26.7	1.00		1.00	
Low-dose TCA	1864	286	30.4	0.99	0.85 to 1.05	0.84	0.69 to 1.02
BZD	412	65	43.9	1.32	1.00 to 1.73	1.05	0.75 to 1.47
Z-drug	2888	399	37.8	1.11	0.96 to 1.30	1.05	0.87 to 1.25
Mortality							
No sleep drug	1651	266	16.9	1.00		1.00	
Low-dose TCA	1942	196	18.1	1.00	0.83 to 1.21	0.89	0.72 to 1.11
BZD	443	66	36.7	1.80	1.35 to 2.39	1.38	0.96 to 1.96
Z-drug	3089	355	27.8	1.43	1.21 to 1.69	1.34	1.10 to 1.64

N/A, not applicable; PY, person-year.

a Adjusted for age^2 and the covariates listed in *Table 2* and *Appendix 2*, *Table 39*, except for forearm fracture, which was also adjusted for eye conditions (ARMD, retinal disorders and glaucoma combined), region as only five categories (South, East, Midlands, North and London), and not adjusted for ethnicity or systolic blood pressure.

The incidence of hip fractures was 5.4 per 100 person-years in those prescribed Z-drugs compared with 3.1 per 100 person-years in those not prescribed medication for sleep disturbance. After adjustment for confounders there was a trend towards an increased risk of hip fracture with Z-drugs (HR 1.59, 95% CI 1.00 to 2.53), but this did not reach statistical significance ($p = 0.052$).

There were few reported fractures of the forearm, wrist or hand, with 2.2 per 100 person-years for the Z-drug group and 1.2 per 100-person years for the no sleep medication group. There was not a statistically significant association between Z-drug use and forearm fractures when adjusted for age and sex, or all potential confounders.

The incidence of falls was 37.8 per 100 person-years in those prescribed Z-drugs compared with 26.7 per 100 person-years for those not prescribed medication for sleep disturbance. There was no statistically significant difference in the risk of falls with Z-drug use when adjusted for age and sex, or all potential confounders.

The mortality rate was 27.8 per 100-person years in the Z-drug group compared with 16.9 per 100 person-years in the no sleep medication group. After adjustment for potential confounders, Z-drug prescription was associated with a 34% (95% CI 10% to 64%) increased risk of mortality.

Generally, the risks of fractures, falls and mortality for Z-drugs were similar to those of BZDs (see *Appendix 5*, *Table 55*). Risk of hip fracture with low-dose TCA appeared similar to that of Z-drugs; however, there was no evidence of increased risk of overall fractures, falls or mortality with low-dose TCA.

There was no evidence that the reported HRs varied over time and there was no evidence of an interaction between Z-drug use and either age, sex, mortality or fractures. Using different parametrisations for age had little impact on the findings (see *Appendix 5*, *Table 56*).

Absolute risks

The absolute annual risks of fractures, hip fractures and mortality in the unexposed group were 7.4%, 3.2% and 15.4%, respectively. These equate to annual risks of 10.2%, 5.0% and 20.1% for fractures, hip fractures and mortality when taking Z-drugs if our estimated risks are causal. This is equivalent to a NNH of 36, 54 and 21, and extra cases per 1000 treated of 28, 18 and 47, respectively.

Dose–response

When examining outcomes by cumulative Z-drug dose, we found that fracture risk increased with cumulative exposure to Z-drugs (*Table 8*). During periods when cumulative prescriptions totalled < 28 DDDs of Z-drugs, equivalent to 56 days at the recommended half-dose in the elderly, there were no excess risks of fractures. For 42–55 prescribed DDDs the HR for a fracture increased to 2.81 (95% CI 1.47 to 5.37).

The picture was similar for hip fractures, with no excess risk when prescribed < 28 DDDs of Z-drugs, rising to a HR of 3.33 (95% CI 1.41 to 7.91) when cumulatively prescribed 42–55 DDDs. There were few forearm, wrist or hand fracture outcomes, but there was evidence of a similar pattern to that of fractures with no risk before 28 DDDs and greater risks after. There was evidence of increased falls risks after > 28 DDDs of Z-drugs had been prescribed, but this association disappeared after 56 DDDs were prescribed. The risk of mortality was generally fairly similar, regardless of cumulative exposure to Z-drugs. In addition, we found no evidence of differences in risk according to whether or not the first Z-drug prescription was PRN (see *Appendix 5, Table 57*).

Infections, cardiovascular and agitation or psychosis outcomes

A total of 1104 patients were reported to have an acute bacterial infection during follow-up, with 86% of these being a UTI or LRTI. Whereas, 188 patients experienced an ischaemic stroke or TIA, 72 patients reported venous thromboembolism and 340 patients were recorded as having incident agitation or psychosis during follow-up.

Table 9 displays the incidence and HRs for infections, cardiovascular and agitation or psychosis outcomes for the different sleep disturbance treatment, relative to no prescription for sleep disturbance, adjusted for age and sex, and adjusted for all potential confounders. Although the incidence of acute bacterial infections was greater at 47.7 compared with 34.7 per 100 person-years in patients receiving Z-drugs compared with no sleep disturbance medications, this association was not statistically significant when adjusted for potential confounders. There was also no statistically significant difference between Z-drug prescription and the rate of UTI and LRTI.

TABLE 8 Adjusted HRs for fractures, falls and mortality, by cumulative Z-drug dose

	Age, sex adjusted			Fully adjusted[a]		
Outcome and DDD of Z-drug	HR	95% CI	Test for trend	HR	95% CI	Test for trend
Fracture						
0	1.00		0.001	1.00		0.002
1–13	0.74	0.39 to 1.41		0.69	0.36 to 1.36	
14–27	0.93	0.56 to 1.53		0.91	0.53 to 1.54	
28–41	1.90	1.15 to 3.11		1.96	1.15 to 3.33	
42–55	2.78	1.54 to 5.04		2.81	1.47 to 5.37	
≥ 56	1.48	1.07 to 2.05		1.53	1.04 to 2.25	
Hip fracture						
0	1.00		0.001	1.00		0.003
1–13	0.83	0.36 to 1.88		0.80	0.35 to 1.84	
14–27	0.58	0.26 to 1.29		0.60	0.26 to 1.35	
28–41	1.83	0.91 to 3.65		1.98	0.97 to 4.01	
42–55	3.30	1.50 to 7.24		3.33	1.41 to 7.91	
≥ 56	1.90	1.18 to 3.06		2.03	1.15 to 3.60	
Forearm fracture						
0	1.00		0.005	1.00		0.16
1–27	0.61	0.17 to 2.26		0.47	0.12 to 1.86	
28–41	4.12	1.40 to 12.06		4.15	1.21 to 14.24	
42–55	2.27	0.42 to 12.15		1.89	0.27 to 13.22	
≥ 56	2.08	1.02 to 4.26		1.37	0.49 to 3.80	
Fall						
0	1.00		0.14	1.00		0.49
1–13	0.93	0.69 to 1.27		0.83	0.60 to 1.14	
14–27	1.11	0.87 to 1.42		1.07	0.83 to 1.39	
28–41	1.49	1.12 to 1.98		1.43	1.06 to 1.94	
42–55	1.70	1.17 to 2.45		1.59	1.08 to 2.34	
≥ 56	1.02	0.82 to 1.25		0.94	0.74 to 1.19	
Mortality						
0	1.00		0.001	1.00		0.11
1–13	1.30	0.91 to 1.87		1.34	0.91 to 1.97	
14–27	1.65	1.23 to 2.22		1.68	1.23 to 2.30	
28–41	1.33	0.93 to 1.91		1.32	0.90 to 1.92	
42–55	1.75	1.14 to 2.67		1.64	1.05 to 2.57	
≥ 56	1.36	1.12 to 1.67		1.21	0.96 to 1.53	

a Adjusted for age[2] and the covariates listed in *Table 2* and *Appendix 2*, *Table 39*, except for forearm fracture, which was also adjusted for eye conditions (ARMD, retinal disorders and glaucoma combined), region as only five categories (South, East, Midlands, North and London), and not adjusted for ethnicity or systolic blood pressure.

TABLE 9 Adjusted HRs for infections, stroke, venous thromboembolism and agitation or psychosis, by sleep disturbance medication

Outcome and sleep medication	Patients (*n*)		Incidence/ 100 PYs	Age, sex adjusted		Fully adjusted[a]	
	Exposed	With outcome		HR	95% CI	HR	95% CI
Acute bacterial infection							
No sleep drug	1303	374	34.7	1.00		1.00	
Low-dose TCA	1423	273	37.8	1.02	0.87 to 1.19	1.00	0.83 to 1.21
BZD	334	49	38.6	0.92	0.68 to 1.24	0.84	0.59 to 1.21
Z-drug	2267	408	47.7	1.17	1.01 to 1.36	1.09	0.92 to 1.29
UTI/LRTI							
No sleep drug	1303	328	29.5	1.00		1.00	
Low-dose TCA	1423	226	31.3	0.96	0.81 to 1.14	0.96	0.78 to 1.18
BZD	334	41	31.5	0.90	0.65 to 1.25	0.85	0.58 to 1.26
Z-drug	2267	354	40.2	1.16	0.99 to 1.36	1.10	0.92 to 1.32
Ischaemic stroke/TIA							
No sleep drug	1640	64	4.2	1.00		1.00	
Low-dose TCA	1933	50	4.7	1.03	0.71 to 1.49	1.20	0.75 to 1.92
BZD	438	15	8.7	1.81	1.01 to 3.26	1.56	0.69 to 3.51
Z-drug	3045	80	6.5	1.45	1.02 to 2.07	1.33	0.85 to 2.07
Venous thromboembolism							
No sleep drug	1648	22	1.4	1.00		1.00	
Low-dose TCA	1940	24	2.2	1.53	0.88 to 2.67	1.23	0.56 to 2.69
BZD	442	< 5	N/A	N/A			
Z-drug	3074	26	2.1	1.53	0.86 to 2.72	1.66	0.69 to 3.98
Incident agitation/psychosis							
No sleep drug	1282	79	6.4	1.00		1.00	
Low-dose TCA	1633	85	9.7	1.36	0.99 to 1.05	1.43	0.96 to 2.13
BZD	313	36	30.5	3.89	2.54 to 5.96	5.61	3.14 to 10.01
Z-drug	2574	140	13.6	1.59	1.20 to 2.11	1.71	1.21 to 2.42

PY, person-year.
a Adjusted for age^2 and the covariates listed in *Table 2* and *Appendix 2, Table 39*.

Although the incidence of ischaemic stroke or TIA was greater at 6.5 compared with 4.2 per 100 person-years in patients receiving Z-drugs compared with no sleep disturbance medications, this association was not statistically significant when adjusted for potential confounders.

There were few venous thromboembolism events and, again, we did not detect a statistically significant difference in their rate between patients prescribed Z-drugs and those not prescribed medications for sleep disturbance.

The incidence of agitation or psychosis in patients prescribed Z-drugs was 13.6 per 100 person-years, compared with 6.4 per 100 person-years for those not prescribed medication for sleep disturbance.

After adjustment for potential confounders, Z-drug prescription was associated with a HR of 1.71 (95% CI 1.21 to 2.42) for agitation or psychosis. There was no evidence that this association varied by age or sex.

There was no association between low-dose TCA and any of the infection, cardiovascular, or agitation or psychosis outcomes. There was a greater incidence of ischaemic stroke or TIA in those prescribed BZDs, but this difference failed to reach statistical significance. BZD prescription was, however, associated with an increased rate of agitation or psychosis.

Dose–response

When examining outcomes by cumulative Z-drug dose, we found some suggestion of increased acute bacterial infections with cumulative exposure to Z-drugs (*Table 10*); however, this was only during periods when cumulative prescriptions totalled 28–41 DDDs and not for > 42 DDDs. There was no evidence of increased risks of ischaemic stroke, TIA, or venous thromboembolism with cumulative Z-drug use. However, the incidence of agitation or psychosis increased with greater cumulative Z-drug prescriptions, such that for 42–55 prescribed DDDs, the HR increased to 2.55 (95% CI 1.31 to 4.98). In addition, we found no evidence of differences in risk according to whether or not the first Z-drug prescription was PRN (see *Appendix 5*, *Table 57*).

Additional medications

A total of 1124 (16%) patients were prescribed a different class of sleep medication during follow-up (*Table 11*). We did not detect a statistically significant increased rate of new medications for sleep disturbance in the Z-drug or BZD groups. Those prescribed low-dose TCA were 79% (95% CI 65% to 97%) less likely to be prescribed another medication for sleep disturbance. The additional sleep medications prescribed are described in *Table 5*.

However, Z-drug users were more likely to be prescribed a new antipsychotic (HR 2.01, 95% CI 1.60 to 2.52), antidepressant (HR 2.05, 95% CI 1.56 to 2.68) and antibiotic during follow-up (HR 1.26, 95% CI 1.12 to 1.42). There was no evidence that these associations varied by age or sex. BZD users had similar increased rates of antipsychotic, antidepressant and antibiotic prescribing to the Z-drug users (see *Appendix 5, Table 58*). No increased rates of antipsychotic or antibiotic prescriptions were detected for low-dose TCA users.

Health-care utilisation

A total of 133,673 GP visits were recorded by the patients in the 2 years following the index date (before 31 March 2016 and before leaving the practice), equivalent to a mean number of visits of 15.9 (SD 20.4). Patients prescribed Z-drugs visited their GP 922 times per 100 person-years, compared with those not prescribed medications for sleep disturbance visiting their GP 783 times per 100 person-years (*Table 12*). After adjusting for potential confounders, Z-drug users visited their GP on average 14% (95% CI 8% to 19%) more frequently over the next 2 years.

A total of 12,850 hospital admissions were recorded by the patients in the 2 years following the index date and before 31 March 2016, equivalent to a mean number of admissions of 1.5 (SD 2.3). Patients prescribed Z-drugs were admitted to hospital 112 times per 100 person-years, compared with 98 times per 100 person-years for those not prescribed medications for sleep disturbance. After adjusting for potential confounders, Z-drug users were admitted to hospital on average 12% (95% CI 3% to 21%) more frequently over the next 2 years.

There was no evidence that these associations varied by age or sex. We also did not detect an increased frequency of GP visits or hospital admission among BZD and low-dose TCA users.

TABLE 10 Adjusted HRs for infections, stroke, venous thromboembolism and agitation or psychosis, by cumulative Z-drug dose

	Age, sex adjusted			Fully adjusted[a]		
Outcome and DDD of Z-drug	HR	95% CI	Test for trend	HR	95% CI	Test for trend
Acute bacterial infection						
0	1.00		0.002	1.00		0.04
1–13	0.82	0.60 to 1.14		0.77	0.55 to 1.08	
14–27	0.93	0.71 to 1.21		0.89	0.68 to 1.17	
28–41	1.44	1.09 to 1.90		1.38	1.04 to 1.84	
42–55	1.18	0.78 to 1.78		1.14	0.74 to 1.74	
≥ 56	1.27	1.06 to 1.53		1.17	0.95 to 1.44	
UTI/LRTI						
0	1.00		0.01	1.00		0.12
1–13	0.87	0.61 to 1.24		0.84	0.58 to 1.21	
14–27	0.96	0.72 to 1.28		0.96	0.71 to 1.29	
28–41	1.46	1.08 to 1.98		1.43	1.04 to 1.95	
42–55	1.12	0.71 to 1.78		1.09	0.68 to 1.75	
≥ 56	1.22	1.00 to 1.49		1.13	0.90 to 1.41	
Ischaemic stroke/TIA						
0	1.00		0.005	1.00		0.11
1–13	0.71	0.29 to 1.74		1.02	0.39 to 2.71	
14–27	1.02	0.54 to 1.92		1.09	0.55 to 2.15	
28–41	1.77	0.92 to 3.39		1.63	0.79 to 3.36	
42–55	0.91	0.27 to 3.06		0.80	0.22 to 2.86	
≥ 56	1.69	1.14 to 2.51		1.48	0.90 to 2.42	
Venous thromboembolism						
0	1.00		0.26	1.00		0.47
1–13	2.08	0.64 to 6.76		1.74	0.55 to 5.56	
14–27	1.83	0.64 to 5.22		1.78	0.50 to 6.32	
28–41	1.30	0.27 to 6.22		1.58	0.29 to 8.50	
≥ 42	1.44	0.72 to 2.85		1.52	0.53 to 4.40	
Incident agitation/psychosis						
0	1.00		0.001	1.00		0.008
1–13	1.09	0.64 to 1.87		1.38	0.76 to 2.48	
14–27	1.45	0.95 to 2.21		1.72	1.08 to 2.74	
28–41	1.42	0.83 to 2.43		1.58	0.89 to 2.80	
42–55	2.31	1.24 to 4.32		2.55	1.31 to 4.98	
≥ 56	1.74	1.20 to 2.52		1.70	1.09 to 2.64	

a Adjusted for age[2] and the covariates listed in *Table 2* and *Appendix 2, Table 39*.

TABLE 11 Adjusted HRs for additional medication prescriptions, by sleep disturbance medication

Outcome and sleep drug	Patients exposed (*n*)	Number of outcomes	Incidence/ 100 PYs	Age, sex adjusted		Fully adjusted[a]	
				HR	95% CI	HR	95% CI
Additional sleep medication							
No sleep drug	1651	336	21.4	1.00		1.00	
Low-dose TCA	1942	258	23.8	0.89	0.75 to 1.05	0.79	0.65 to 0.97
BZD	443	45	25.0	0.76	0.56 to 1.05	0.63	0.43 to 0.93
Z-drug	3089	485	38.0	1.26	1.08 to 1.46	1.13	0.95 to 1.35
Incident antipsychotic prescription							
No sleep drug	1291	175	13.8	1.00		1.00	
Low-dose TCA	1618	164	19.1	1.13	0.90 to 1.40	1.17	0.90 to 1.53
BZD	375	66	59.5	2.37	1.75 to 3.21	2.23	1.50 to 3.32
Z-drug	2402	355	39.5	2.03	1.67 to 2.47	2.01	1.60 to 2.52
Incident antidepressant prescription							
No sleep drug	1207	113	10.3	1.00		1.00	
BZD	326	31	24.4	1.75	1.17 to 2.64	1.77	1.02 to 3.09
Z-drug	2177	236	28.3	2.04	1.61 to 2.57	2.05	1.56 to 2.68
Incident antibiotic prescription							
No sleep drug	1364	616	69.8	1.00		1.00	
Low-dose TCA	1552	562	93.8	1.21	1.08 to 1.36	1.13	0.99 to 1.29
BZD	357	116	120.8	1.38	1.12 to 1.70	1.35	1.06 to 1.71
Z-drug	2430	818	116.4	1.39	1.25 to 1.55	1.26	1.12 to 1.42

PY, person-year.
a Adjusted for age^2 and the covariates listed in *Table 2* and *Appendix 2, Table 39*.

TABLE 12 Adjusted IRRs for health-care utilisation, by sleep disturbance medication

Outcome and sleep drug	Patients exposed (*n*)	Number of outcomes	Incidence/ 100 PYs	Age, sex adjusted		Fully adjusted[a]	
				IRR	95% CI	IRR	95% CI
Number of GP visits							
No sleep drug	1651	25,610	783.2	1.00		1.00	
Low-dose TCA	1942	33,530	882.1	1.22	1.15 to 1.30	1.01	0.96 to 1.07
BZD	443	6806	791.4	1.12	1.02 to 1.23	1.05	0.97 to 1.14
Z-drug	3089	47,259	922.5	1.24	1.17 to 1.31	1.14	1.08 to 1.19
Number of hospital admissions							
No sleep drug	1651	2484	99.7	1.00		1.00	
Low-dose TCA	1942	2991	105.2	1.08	0.97 to 1.19	1.04	0.95 to 1.15
BZD	443	614	98.9	1.00	0.87 to 1.16	0.97	0.84 to 1.13
Z-drug	3089	4836	112.3	1.15	1.05 to 1.26	1.12	1.03 to 1.21

PY, person-year.
a Adjusted for age^2 and the covariates listed in *Table 2* and *Appendix 2, Table 39*.

Multiple testing

Owing to the number of outcomes tested, we would expect some associations to be statistically significant by chance alone. For the association between Z-drug prescription and the 16 outcomes, we estimated a critical threshold of $p < 0.02$ to define statistical significance, such that the false discovery rate was < 5%. Of the 16 outcomes tested, the outcomes of mortality, agitation or psychosis, antipsychotics, antidepressants, antibiotics, GP visits and hospital admissions, all had associations with Z-drug use with $p < 0.02$ and, hence, can be considered statistically significant after accounting for the multiple tests performed. However, the observed association with fractures, with $p = 0.045$, would not be considered statistically significant and has an increased chance of being a false discovery. However, multiple testing procedures vary as to how they define statistical significance and assume that all outcomes are independent events, which may not be the case here. Regardless, with a *p*-value so close to 0.05 for fractures, it would not pass any multiple testing correction. Our findings need interpretation within this context (i.e. the association between Z-drug prescription and fractures could be a chance finding due to many outcomes tested). The fracture finding needs to be considered in the context of its consistency with findings for other outcomes (e.g. specific fractures, falls), consistency within cumulative dose–response relationships, as well as evidence from other studies.

Sensitivity analysis: missing data

Data were missing for smoking status (for 3% of patients), alcohol use (for 9% of patients), recent BMI (for 32% of patients), systolic blood pressure (for 2% of patients), care home status (for 34% of patients) and quantity of tablets prescribed (for < 0.01% of those prescribed Z-drugs). Below, we explore the consequences of missing data for BMI and care home status, as these variables are missing for > 10% of patients.

Body mass index values were not missing completely at random. Those without a BMI measurement in the last 5 years were more likely to be older, to be living in a care home, to visit their GP less often, to have fewer comorbidities, fewer prescriptions and immunisations, to have had dementia for longer with a history of agitation or psychosis, and to be from a less deprived area. Recent BMI was also more likely to be recorded in the no sleep drug cohort. Associations between Z-drug use and the adverse events varied in the patients with and without missing BMI data. For example, the HR for fractures adjusted only for age and sex was 1.13 (95% CI 0.71 to 1.79) and was 1.56 (95% CI 1.12 to 2.18) in those with and without missing BMI data.

Care home status was also not missing completely at random. Patients missing their care home status were more likely to be younger, male and to have fewer comorbidities and prescriptions, except for more lipid-lowering medications and inhaled corticosteroids. Again, care home status was more likely to be recorded in the no sleep drug cohort. Associations between Z-drug use and the adverse events varied in the patients with and without missing care home data. For example, the HR for fractures adjusted only for age and sex was 1.35 (95% CI 0.99 to 1.83) and was 1.73 (95% CI 0.98 to 3.06) in those with and without care home status recorded.

A single imputation model recoded 429 (15%) of those with missing care home status as being in a care home, and the rest as not. Subsequently, a single imputation model including information from BMI values more than 5 years ago, recategorised 26 (1%), 1598 (69%), 594 (26%), and 87 (4%) patients with recent BMI missing into values of < 18.5, 18.5–24.9, 25–29.9, and ≥ 30 kg/m^2, respectively. Adjustment for all the covariates included the imputed BMI and care home variables, had little effect on estimates (see *Appendix 5*, *Tables 59* and *60*).

Sensitivity analysis: sleep disturbance definition

When excluding diagnoses of sleep disturbance in the GP records if they were accompanied by record of a 'satisfactory' sleep pattern, only 924 (56%) of the patients in the no sleep medication cohort met this criterion. These 924 patients were more likely to have a recent fracture, dizziness, faint, hospitalisation, agitation or psychosis, antipsychotic prescription and to be from less deprived neighbourhoods, and were less likely to have urinary incontinence, a history of insomnia, to drink alcohol or be in a care home, than those with record of satisfactory sleep disturbance. Comparing to this group generally decreased the associations with Z-drug use and the various outcomes (see *Appendix 5*, *Tables 61* and *62*). The HR between Z-drug use and fracture, hip fracture and mortality reduced to 1.34 (95% CI 0.90 to 1.99), 1.33 (95% CI 0.77 to 2.32) and 1.09 (95% CI 0.86 to 1.38), respectively.

Sensitivity analysis: Clinical Practice Research Datalink records only

Appendix 5, *Table 63*, displays the main analyses when the adverse event outcomes are ascertained only through the CPRD. In general, omission of the HES- and ONS-linked data resulted in fewer outcomes, particularly for the Z-drug group than the no sleep medication group. Consequently, associations between Z-drug use and the outcomes were attenuated closer to the null.

Our main analysis included 368 incident fractures, yet restricting outcome ascertainment to CPRD only reduced this to 262 fractures (71%). The number of fractures in the Z-drug group reduced by 67% and in the no sleep medication group by 77%, and this deceased the resulting adjusted HR from 1.40 to 1.27. Similarly, the number of incident hip fractures reduced to 61% of that in the main analysis in the Z-drug group and to 74% in the no sleep medication group, leading to a reduced adjusted HR from 1.59 to 1.38. Besides incident agitation or psychosis, for which only 9% fewer outcomes occur when restricting to CPRD, all the other adverse events have a reduction of around 28–45% in the number of outcomes recorded.

Sensitivity analysis: discontinuing Z-drugs

The 1274 patients who discontinued Z-drugs generally experienced fewer adverse events in the preceding period than the 3089 patients who were initiated on Z-drugs. Those initiating Z-drugs had higher rates of falls, mortality, infections and agitation or psychosis than those who had just discontinued Z-drugs (see *Appendix 5, Table 64*). Although the rates of fractures were lower when discontinuing Z-drugs, these differences did not reach statistical significance. Rates of new antipsychotic, antidepressant and antibiotic prescribing were lower in those discontinuing Z-drugs.

Chapter 6 Clinical cohort studies results

The REDIC study results

Participant characteristics

Of the 696 participants recruited to the REDIC study, 17 participants had no dementia or MCI at baseline and one participant did not provide enough information at their baseline assessment to be included in the current analysis. Therefore, these participants were excluded from the current analysis, leaving 95 participants with MCI and 583 participants with dementia at baseline.

The number with usable assessments at each wave, along with the prevalence of use of each hypnotic reported at each wave, is shown in *Appendix 3*, *Table 42*. Forty-two per cent of the sample gave assessments at visit 5 (2 years after baseline). The rate of Z-drug and BZD use was high, with around 20% of participants reporting Z-drug use, 20% reporting BZDs and up to 20% reporting antipsychotics at each visit. Antidepressants were also widely used (30–40% of participants at each wave), with lower numbers reporting antihistamines or antiepileptics. The distribution of key outcome measures and dementia severity at baseline stratified by Z-drug, BZD and antipsychotic use is shown in *Table 13*.

The vast majority of those who left the study between waves had died, but some had refused to continue, were withdrawn by their nursing home, moved home or had moved to a nursing home not participating in the REDIC study.

TABLE 13 Participant characteristics at study entry, stratified by CDR-global rating

	Dementia severity, *n* (%)				
Participant characteristics	All	Very mild	Mild	Moderate	Severe
Sex (female)	415 (64.4)	49 (65.3)	108 (65.1)	187 (68.8)	71 (54.2)
Marital status					
Unmarried	57 (8.9)	7 (9.5)	15 (9.1)	24 (8.9)	11 (8.5)
Married	194 (30.5)	19 (25.7)	45 (27.4)	80 (29.7)	50 (38.5)
Widowed or divorced	386 (60.6)	48 (64.9)	104 (63.4)	165 (61.3)	69 (53.1)
Years of education					
0–6	25 (3.9)	2 (2.7)	7 (4.2)	12 (4.4)	4 (3.1)
7	212 (32.9)	21 (28)	51 (30.7)	102 (37.5)	38 (29)
8–12	216 (33.5)	34 (45.3)	65 (39.2)	84 (30.9)	33 (25.2)
≥ 13	191 (29.7)	18 (24)	43 (25.9)	74 (27.2)	56 (42.7)
Age group (years)					
< 69	26 (4)	1 (1.3)	10 (6)	10 (3.7)	5 (3.8)
70–79	115 (17.9)	8 (10.7)	24 (14.5)	50 (18.4)	33 (25.2)
80–89	318 (49.4)	38 (50.7)	92 (55.4)	130 (47.8)	58 (44.3)
≥ 90	185 (28.7)	28 (37.3)	40 (24.1)	82 (30.1)	35 (26.7)

continued

TABLE 13 Participant characteristics at study entry, stratified by CDR-global rating (*continued*)

Participant characteristics	Dementia severity, *n* (%)				
	All	Very mild	Mild	Moderate	Severe
Medication use					
Z-drug	120 (18.6)	26 (34.7)	32 (19.3)	49 (18.0)	13 (9.9)
BZD	101 (15.7)	23 (30.7)	25 (15.1)	30 (11)	23 (17.6)
Antipsychotics	83 (12.9)	7 (9.3)	18 (10.8)	35 (12.9)	23 (17.6)
Antihistamines	24 (3.7)	3 (4)	6 (3.6)	9 (3.3)	6 (4.6)
Antidepressants	190 (29.5)	24 (32)	43 (25.9)	81 (29.8)	42 (32.1)
Antiepileptics	33 (5.1)	5 (6.7)	8 (4.8)	8 (2.9)	12 (9.2)
Indications[a]					
Anxiety	214 (33.4)	21 (28)	43 (25.9)	91 (33.6)	59 (46.1)
Agitation/aggression	196 (30.7)	6 (8)	34 (20.7)	87 (32.1)	69 (53.9)
Sleep disturbance	183 (28.7)	13 (17.6)	37 (22.4)	84 (31.1)	49 (38)

a Anxiety, agitation/aggression and sleep disturbance are measured by any non-zero NPI frequency/severity value.

Dynamics of hypnotic use throughout the study

The ability to estimate the effect of hypnotics is ultimately derived from within-person comparisons of hypnotic use compared with no hypnotic use. Hence, the number of transitions between hypnotic use and no hypnotic use within individuals between visits is crucial. The number of such transitions is shown for Z-drugs, BZDs and antipsychotics in *Table 14*, between each of the 1540 pairs of consecutive visits in the REDIC study data set. There is a positive correlation between use of pairs of medications (e.g. out of 421 occasions where Z-drugs were reported, BZDs were also reported on 126 occasions) (*Table 15*).

Predictors of dropout and mortality

A logistic regression model was applied with drop-out at the next wave as the outcome, and hypnotic use, outcomes and demographics covariates as predictors (see *Appendix 3*, *Table 43*). The vast majority of dropouts from the study were due to death and so the different forms of outcome were not modelled individually. Clustered standard errors were used to account for multiple data points per individual contributing to this analysis.

TABLE 14 The number of participants who start, stop, continue or do not use hypnotics between visits

Medication	No use at previous visit, *n* (%)			With use at previous visit, *n* (%)		
	Total	No use	Starting	Total	Stopping	Continuous use
Z-drugs	1259 (100)	1175 (93)	84 (7)	281 (100)	70 (25)	211 (75)
BZDs	1224 (100)	1121 (92)	93 (8)	316 (100)	76 (24)	240 (76)
Antipsychotics	1295 (100)	1214 (94)	81 (6)	245 (100)	61 (25)	184 (75)

Note
Percentages are based on the numbers who use or do not use hypnotics at previous visit, so reflect the rate of stopping or starting each drug.

TABLE 15 Pairwise association between use of Z-drugs, BZDs and antipsychotics in all REDIC study visits

	Z-drugs	BZDs	Antipsychotics
Z-drugs	421	126	78
BZDs	2.0 (1.6 to 2.6)	440	122
Antipsychotics	1.3 (0.95 to 1.7)	2.6 (2.0 to 3.4)	349

Note
Diagonal cells contain the total number of occasions among all visits on which each medication was reported, numbers to the right of the diagonal represent the number of occasions on which each pairwise combination was reported and numbers to the left of the diagonal contain the OR (95% CI), representing the association between the use of each class.

After adjusting for covariates, those who used Z-drugs were less likely to complete the next assessment (OR 1.47, 95% CI 1.03 to 2.09), although those using BZDs were more likely. Antipsychotic use did not predict subsequent loss to follow-up independently of disability and cognitive function (as measured with CDR-global). Those who were more severely disabled or older were more likely to be lost, but net of this there was no clear link between dropout and cognitive function. There was little association between neuropsychiatric symptoms and subsequent loss to follow-up.

Predictors of hypnotic use

Tables 14 and *15* show that medication use at a previous wave is an extremely strong predictor of medication use at the current wave. Hence, for each medication of interest two logistic models were estimated, one for stopping and another for starting, conditional on participant characteristics and lagged values of time-varying covariates. Clustered standard errors were used to account for multiple data points per individual contributing to this analysis.

Table 16 shows the independent predictors of starting (current use conditional on no prior use) and *Appendix 3*, *Table 44*, shows the factors predicting continuing medication use (current use conditional on prior use) estimated using these models, which are also used to identify confounding variables to develop the marginal structural model analysis below.

Z-drugs and BZDs are more commonly started among those with less severe dementia, more strikingly so for Z-drugs than for BZDs. Conversely, antipsychotics are more commonly started among those with more severe dementia. Prior use of Z-drugs predicts new use of BZDs. Prior levels of neuropsychiatric symptoms independently predict new use of hypnotics, in particular prior sleep disturbance predicts new Z-drug and BZD use, anxiety predicts new use of all three classes. However, a considerable number of participants started Z-drugs without having any prior sleep disturbance, anxiety or agitation recorded in any previous assessment (not shown).

There were fewer clear predictors of continuing hypnotic use (equivalently of stopping use) between visits. In particular, levels of neuropsychiatric symptoms and dementia severity were not significantly linked to use of any hypnotic if there was use at a previous wave.

Dynamics of outcome measures and estimating the effect of hypnotic use on outcome measures

Figures 13–22 in *Appendix 3* describe how each outcome measure changes between waves and vary with age, CDR stage and with concurrent Z-drug use. The left-hand panels of *Figures 3–12* show how outcome measures change with changing hypnotic use status. The right-hand panels of *Figures 3–12* show the association between current hypnotic use and outcome measures, with weights applied to each observation such that levels of previous hypnotic use, cognitive function and neuropsychiatric variables are balanced between those currently using each medication and those not using each medication. Thus, these graphs show the effect of current medication use controlling for key patient characteristics,

TABLE 16 Association between clinical and demographic factors and starting hypnotics at the next visit, among those with no use at the current visit

	Starting Z-drugs		Starting BZDs		Starting antipsychotics	
Participant characteristics	OR	95% CI	OR	95% CI	OR	95% CI
Age (years)						
< 70	0.59	0.14 to 2.46	1.37	0.47 to 4.00	0.82	0.30 to 3.78
70–79	Ref		Ref		Ref	
80–89	1.29	0.66 to 2.54	0.97	0.51 to 1.85	0.51*	0.25 to 1.25
≥ 90	0.76	0.34 to 1.73	0.75	0.33 to 1.67	0.46	0.23 to 1.39
Dementia severity						
Minimal	5.31***	2.15 to 13.12	3.09*	1.30 to 7.34	0.37	0.22 to 2.75
Mild	1.19	0.49 to 2.91	1.47	0.70 to 3.11	0.53	0.37 to 2.23
Moderate	1.50	0.73 to 3.09	0.86	0.44 to 1.67	0.51*	0.28 to 1.18
Severe	Ref		Ref		Ref	
Sex (female)	1.46	0.85 to 2.52	1.07	0.63 to 1.81	1.18	0.47 to 2.03
Marital status						
Unmarried	Ref		Ref		Ref	
Married	3.92	0.90 to 17.06	1.54	0.59 to 3.97	0.51	0.2 to 1.59
Widowed/divorced	4.74*	1.07 to 20.92	1.44	0.54 to 3.87	0.64	0.25 to 1.71
Hypnotic use						
BZDs	1.22	0.67 to 2.21			0.99	0.28 to 1.28
Z-drugs			1.64	0.92 to 2.91	1.20	0.52 to 2.37
Antipsychotics	1.45	0.76 to 2.77	0.54	0.25 to 1.17		
Neuropsychiatric symptoms						
Sleep	1.86***	1.43 to 2.42	1.05	0.76 to 1.44	1.14	0.92 to 1.76
Anxiety	1.63*	1.08 to 2.44	1.59*	1.10 to 2.30	1.59*	1.52 to 3.67
Agitation	0.63	0.37 to 1.08	1.55	0.97 to 2.48	1.22	0.89 to 2.21
Disability (Lawton Physical Self-Maintenance Scale), per unit	1	0.95 to 1.05	0.99	0.94 to 1.04	1.01	0.93 to 1.08
Years in education						
< 7	2.95	0.95 to 9.19	0.91	0.27 to 3.09	0.65	0.13 to 3.71
7	1.05	0.53 to 2.09	0.62	0.33 to 1.17	0.91	0.37 to 1.65
8–11	1.39	0.73 to 2.65	0.69	0.38 to 1.28	0.84	0.30 to 1.33
≥ 12	Ref		Ref		Ref	
Type of admission						
Long stay	Ref		Ref		Ref	
Short stay	0.96	0.49 to 1.87	1.80	1.00 to 3.27	0.78	0.40 to 2.10
Nursing	1.83	0.55 to 6.03	0.69	0.16 to 2.91	0.71	0.13 to 3.89

*$p < 0.05$, ***$p < 0.001$.
Ref, reference.

in particular those characteristics that predict new or continuing medication use at the previous wave. The difference in current mean levels of outcomes between groups can then be interpreted as the effect of the medication, although when weights do not cause prior levels to perfectly coincide, comparing the change over time between groups may better estimate the effect.

Cognitive measures

With respect to cognitive outcomes, *Appendix 3, Figures 3–5* (SIB-8, MMSE and CDR-SOB), shows that those who use Z-drugs tend to have better cognitive function than average, those who use antipsychotics have worse cognitive function than average, but different patterns of changing status are not consistently associated with different levels of decline in cognitive function between assessments. That is, rates of decline between assessments do not appear to be systematically different between those who use no hypnotics, those who start or stop between assessments or those who use hypnotics at both assessments.

Table 17 quantifies these associations, while adjusting for age, the specific visit at which the cognitive assessment is made and baseline cognitive function. There is some evidence for more decline in SIB-8 score among those starting BZDs compared with no use, and some worsening by CDR-SOB among those starting antipsychotics compared with no use. However, these changes are not reflected in other cognitive scores and are not seen among those starting Z-drugs compared with those with no use. When cognitive measures are combined there is no evidence for any additional decline with starting or continuing Z-drug use.

Appendix 3, Figures 3–5 and *Table 45* (first column), shows the change in cognitive function between waves for Z-drug users compared with non-users, using IPTW to balance the prior cognitive function and neuropsychiatric symptoms between groups. Again, these show no effect of any hypnotic on cognitive function. There is some suggestion that the change in CDR-SOB scores is around 0.5 points higher for those using hypnotics, but this is

TABLE 17 Association between patterns of hypnotic use and change in mean measures of cognitive function and disability between visits, adjusted for baseline age, baseline cognitive function and visit number

	Measure, β (95% CI)			
Exposure	MMSE	CDR-SOB	SIB-8	Disability scale
Z-drug				
No use	Ref	Ref	Ref	Ref
Starting	0.01 (–1.44 to 1.46)	–0.17 (–0.88 to 0.55)	–0.58 (–1.72 to 0.55)	–0.05 (–0.72 to 0.61)
Stopping	–0.51 (–2.04 to 1.01)	0.53 (–0.18 to 1.24)	–0.94 (–2.26 to 0.37)	0.53 (–0.38 to 1.44)
Continuing	0.65 (–0.06 to 1.36)	–0.14 (–0.51 to 0.24)	–0.13 (–0.68 to 0.42)	–0.54** (–0.94 to –0.15)
BZD				
No use	Ref	Ref	Ref	Ref
Starting	–0.36 (–1.83 to 1.11)	0.78** (0.20 to 1.37)	0.60 (–0.25 to 1.45)	0.02 (–0.61 to 0.65)
Stopping	0.82 (–0.37 to 2.01)	–0.37 (–0.99 to 0.25)	0.40 (–0.67 to 1.47)	–0.12 (–0.89 to 0.65)
Continuing	0.44 (–0.20 to 1.08)	–0.07 (–0.43 to 0.29)	0.20 (–0.30 to 0.70)	–0.30 (–0.67 to 0.08)
Antipsychotic				
No use	Ref	Ref	Ref	Ref
Starting	–1.39** (–2.41 to –0.36)	0.33 (–0.25 to 0.91)	–0.49 (–1.35 to 0.37)	0.91 (–0.05 to 1.86)
Stopping	–0.42 (–1.79 to 0.94)	0.36 (–0.27 to 0.98)	–0.03 (–0.96 to 0.90)	0.11 (–0.60 to 0.82)
Continuing	0.05 (–0.63 to 0.74)	–0.06 (–0.44 to 0.33)	0.20 (–0.39 to 0.79)	0.33 (–0.10 to 0.77)

**$p < 0.01$.
Ref, reference.

only statistically significant for BZDs and there is no effect on any other cognitive measure. Fixed-effects linear models (see *Appendix 3*, *Table 45*) comparing occasions with hypnotic use with those without within each participant yield similar results in the whole cohort, and when restricted to those not using any hypnotics at baseline and among those with mild dementia at baseline.

Sleep disturbance

As seen in *Cognitive measures*, participants with a sleep disturbance are more likely to start Z-drugs at the next wave than any other group. This is reflected in *Appendix 3, Figure 6*, which shows that those who start Z-drugs have higher prior values of sleep disturbance than each of the other groups. There is a subsequent decline in sleep disturbance among this group compared with those who do not use Z-drugs; however, when corrected for baseline sleep disturbance using IPTW weighting, this effect is no longer apparent. In fact, there is some evidence for an increase in sleep disturbance associated with Z-drug use. Fixed-effects models show no effect of Z-drugs on sleep after adjusting for between-patient differences.

There are no significant associations between antipsychotics, BZD use and sleep disturbance in any of the models estimated (see *Appendix 3*, *Table 46*).

Anxiety and agitation

Those using BZDs and antipsychotics, or those starting or stopping between waves, had higher levels of anxiety and agitation than those who did not use either drug (see *Appendix 3*, *Figures 7* and *8*). There was no such association with Z-drugs. There was also was no significant difference in the change in anxiety or agitation scores in any group compared with those not using hypnotics, except for an apparent decline in agitation among those continuously using antipsychotics compared with each other group. This difference was also seen using IPTW models, along with an increase in anxiety among antipsychotic users compared with those not using antipsychotics and an increase in agitation scores among BZD users (see *Appendix 3*, *Table 46*).

Quality of life and disability

Although few associations were statistically significant, use of any hypnotic medication appears associated with lower QoL scores when measured by VAS (see *Appendix 3*, *Figure 9*), EQ-5D questions (see *Appendix 3*, *Figure 10*) or the QUALID scale (see *Appendix 3*, *Figure 11*). This finding is consistent across models (see *Appendix 3*, *Table 45*).

When patterns of starting or stopping are considered, there is some evidence that starting Z-drugs is associated with lower QoL, but it is not statistically significant. Both stopping and starting antipsychotics was associated with worse QoL compared with no use at either wave (see *Appendix 3*, *Table 47*).

Disability is correlated with CDR-SOB (Spearman's $r = 0.52$) and the effect of hypnotics on disability follows a similar pattern. Those using antipsychotics are more disabled and there is some evidence that those starting antipsychotics become more disabled than those who do not use them, although this is not statistically significant except under the fixed-effect model including all participants (see *Appendix 3*, *Figure 12* and *Table 17*). There is no evidence for any impact of Z-drug use on disability.

The NACC data set results

Participant characteristics

The distribution of the characteristics of the 17,055 people living with dementia on study entry (defined as their first assessment with a record of dementia) stratified by baseline CDR-global is shown in *Table 18*. The median year of joining the study is 2009 and the median age is 76 (range 21–110, IQR 67–82) years. Fifty-two per cent of the cohort were female. There is little association between age at study entry and dementia stage at entry. Although most participants join the study at dementia stage ≤ 1, 14% joined at CDR 2 (moderate dementia) and 8% at CDR 3 (severe dementia).

TABLE 18 Description of the NACC data set sample at first visit with a study diagnosis of dementia, stratified by dementia severity

Participant characteristics	Dementia severity (CDR stage)			
	Minimal (CDR < 1)	Mild (CDR = 1)	Moderate (CDR = 2)	Severe (CDR = 3)
n	6070	7315	2371	1299
Year, median (IQR)	2010 (2007–2013)	2009 (2007–2012)	2008 (2006–2011)	2008 (2006–2011)
Female, *n* (%)	3064 (50)	3768 (52)	1334 (56)	755 (58)
Age (years), median (IQR)	74 (67–81)	76 (67–82)	76 (67–83)	76 (66–83)
Drug use, *n* (%)				
Z-drug	146 (2)	149 (2)	39 (2)	39 (3)
BZD	401 (7)	492 (7)	194 (8)	189 (15)
Antipsychotic	163 (3)	466 (6)	382 (16)	443 (35)
Antidepressant	2122 (35)	2983 (41)	1049 (45)	588 (47)
Medication data missing	57 (1)	57 (1)	35 (1)	39 (3)
Cognitive function				
Delta trail time, mean (SD)	133.9 (76.0)	155.7 (73.6)	170.0 (59.9)	130.0 (94.6)
Delta trail time data missing, *n* (%)	1245 (21)	2905 (40)	1756 (74)	1242 (96)
Animal fluency, median (IQR)	12 (9–16)	10 (7–13)	6 (3–9)	2 (0–4)
Animal fluency data missing, *n* (%)	374 (6)	618 (8)	627 (26)	934 (72)
MMSE, median (IQR)	25 (22–27)	22 (18–25)	14 (9–19)	0 (0–7)
MMSE data missing, *n* (%)	953 (16)	1016 (14)	269 (11)	163 (13)
CDR-SOB, median (IQR)	3 (2–3.5)	5.5 (4.5–6.5)	11 (10–12)	18 (16–18)
CDR-SOB data missing, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)
Neuropsychiatric symptoms				
Sleep disturbance, *n* (%)	1526 (26)	2282 (32)	876 (38)	473 (41)
Sleep disturbance data missing, *n* (%)	226 (4)	270 (4)	92 (4)	158 (12)
Anxiety, *n* (%)	1940 (33)	3006 (43)	1110 (49)	517 (45)
Anxiety data missing, *n* (%)	218 (4)	262 (4)	91 (4)	155 (12)
Agitation, *n* (%)	1593 (27)	2544 (36)	1079 (47)	610 (53)
Agitation data missing, *n* (%)	216 (4)	257 (4)	89 (4)	155 (12)
NPI excluding sleep, mean (SD)	3.47 (3.64)	5.12 (4.57)	6.98 (5.33)	7.60 (5.95)
NPI excluding sleep data missing, *n* (%)	226 (4)	270 (4)	92 (4)	158 (12)
Other outcomes				
GDS, median (IQR)	2 (1–4)	2 (1–4)	2 (1–4)	2 (1–5)
GDS data missing, *n* (%)	330 (5)	687 (9)	579 (24)	999 (77)
Disability, median (IQR)	7 (4–12)	16 (11–21)	26 (22–29)	30 (29–30)
Disability data missing, *n* (%)	195 (3)	190 (3)	63 (3)	61 (5)

Note
Under each variable, number missing indicates the number and proportion of participants for whom each measure is not available.

The reported prevalence of Z-drug and BZD use is far lower in NACC data set than in the REDIC study cohort. Only 2–3% of participants report Z-drug use, whereas 7–15% report BZD use, with highest levels of use among those with severe dementia. Antipsychotic use increases markedly with dementia severity, from 3% (CDR < 1) to 34% (CDR = 3). A substantial proportion of participants at all stages (35–45%) report use of an antidepressant. On fewer than 2% of visits the medication use form was not completed (3% among CDR 3 patients).

Neuropsychiatric symptoms are reported relatively frequently at all stages. Some sleep disturbance is reported for 26–41% of participants across groups; anxiety and agitation have similar numbers. These assessments are present for 96% of participants in CDR stages 0.5–2 and 88% at CDR stage 3. The average total NPI symptom score excluding sleep disturbance increases from 3.5 to 7.6 with dementia severity.

Average disability score increases with dementia severity, such that almost all of those with severe dementia score 29 or 30 out of 30 on the disability scale. In contrast, the level of depression is generally low (median GDS 2/10, IQR 1–4), but in severe dementia 77% of participants are not able to complete the GDS.

The number of participants completing each annual visit is shown in *Appendix 4*, *Table 48*. Only 9889 (59%) participants complete more than one visit, 4020 (24%) of participants complete visit 4, whereas only 838 (5%) complete visit 7. Prevalence of Z-drugs does not change markedly with visit number, whereas antipsychotics become more common at later visits.

Dynamics of hypnotic use

The numbers of participants starting and stopping Z-drugs, BZDs and antipsychotics between pairs of consecutive visits are shown in *Appendix 4*, *Table 49*. Only 1% of visits report new Z-drug use, although this still corresponds to 219 instances of new Z-drug use, which is a reasonable number from which to estimate changes in outcome measures. Of those who use Z-drugs and return medication data at a subsequent visit, 51% still report Z-drug use. For antipsychotics, the rate of new use (6%) and continuing use (79% of antipsychotic users still use antipsychotics at the next wave) is higher.

Predictors of starting or stopping hypnotics between waves

Table 19 and *Appendix 4, Table 50*, show the independent effects of cognitive function, neuropsychiatric variables and demographic factors at each visit on the use of hypnotics at the subsequent visit, conditional on current hypnotic use.

Among those not using Z-drugs, sleep disturbance did predict new use of Z-drugs at the next wave, but was only slightly linked to new BZD use and was not independently linked to new antipsychotic use. Conversely, anxiety and agitation predicted new use of antipsychotics and BZDs at the subsequent visit. Cognitive function did not predict new use of Z-drugs, but those with more severe dementia were more likely to start BZDs and antipsychotics (see *Table 19*). Independently of cognitive function and symptoms, older people with dementia were less likely to start BZD or antipsychotics, but there was no age effect with Z-drugs.

Among those using hypnotics there were very few variables that were able to predict which participants continued to report hypnotics at the next visit (see *Appendix 4*, *Table 50*). Older people and those with more severe cognitive impairment appeared less likely to continue BZDs, but, crucially, current levels of psychiatric symptoms did not predict whether or not current medications were continued.

Predictors of dropout in the NACC data set

As in the REDIC study, medication use did not strongly predict whether or not each participant completed a subsequent assessment, but older and more severely impaired participants were more likely to drop out. Psychiatric symptoms also did not predict dropout. Note, we do not distinguish dropout through leaving the study, death or censoring and so this should not be interpreted as an assessment of the risk of hypnotics on any outcome.

TABLE 19 The ORs showing the predictors of new use of hypnotics among those not using each drug at the prior wave

	Starting drug at next wave, β (95% CI)		
Factor	Z-drug	BZD	Antipsychotic
Drug use			
Z-drug		2.31*** (1.62 to 3.30)	1.10 (0.73 to 1.67)
BZD	1.97** (1.30 to 2.99)		1.76*** (1.46 to 2.12)
Antipsychotic	1.48 (0.96 to 2.28)	1.61*** (1.33 to 1.96)	
Education (per year)	0.97 (0.92 to 1.01)	1.03*** (1.01 to 1.06)	1.01 (0.99 to 1.03)
Sex (female)	1.11 (0.83 to 1.48)	1.06 (0.92 to 1.23)	0.81*** (0.71 to 0.91)
CDR			
Minimal	1 (Ref)	1 (Ref)	1 (Ref)
Mild	0.85 (0.60 to 1.21)	1.25* (1.02 to 1.52)	2.22*** (1.85 to 2.67)
Moderate	1.10 (0.73 to 1.65)	1.94*** (1.56 to 2.41)	4.63*** (3.81 to 5.62)
Severe	0.83 (0.50 to 1.37)	2.17*** (1.70 to 2.78)	4.02*** (3.20 to 5.04)
Age (years)			
< 61	1 (Ref)	1 (Ref)	1 (Ref)
61–70	1.44 (0.87 to 2.38)	0.76** (0.62 to 0.93)	0.82* (0.69 to 0.98)
71–80	1.22 (0.75 to 2.00)	0.58*** (0.48 to 0.70)	0.73*** (0.62 to 0.86)
81–90	1.06 (0.62 to 1.81)	0.46*** (0.36 to 0.58)	0.58*** (0.47 to 0.70)
≥ 90	1.38 (0.48 to 3.92)	0.46** (0.27 to 0.79)	0.51** (0.33 to 0.80)
Sleep			
None	1 (Ref)	1 (Ref)	1 (Ref)
Mild	1.43 (0.98 to 2.09)	1.21* (1.01 to 1.45)	1.15 (0.99 to 1.34)
Moderate	1.89** (1.28 to 2.80)	1.13 (0.92 to 1.38)	1.13 (0.95 to 1.33)
Severe	2.08** (1.20 to 3.59)	1.09 (0.79 to 1.50)	1.02 (0.78 to 1.32)
Anxiety			
None	1 (Ref)	1 (Ref)	1 (Ref)
Mild	0.74 (0.52 to 1.07)	1.29** (1.09 to 1.53)	1.18* (1.03 to 1.36)
Moderate	0.76 (0.49 to 1.17)	1.81*** (1.50 to 2.18)	1.47*** (1.25 to 1.72)
Severe	1.00 (0.53 to 1.88)	1.74*** (1.26 to 2.40)	1.86*** (1.44 to 2.40)
Agitation			
None	1 (Ref)	1 (Ref)	1 (Ref)
Mild	1.07 (0.76 to 1.51)	1.08 (0.90 to 1.28)	1.49*** (1.30 to 1.71)
Moderate	0.59* (0.36 to 0.97)	1.36** (1.12 to 1.66)	1.73*** (1.47 to 2.03)
Severe	1.04 (0.55 to 1.95)	1.67*** (1.24 to 2.26)	2.77*** (2.16 to 3.54)

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
Ref, reference.

Distribution and dynamics of outcome measures

Appendix 4, *Figures 23–32*, describes how each outcome measure changes between waves and varies with age, CDR stage and with concurrent Z-drug use. Delta trail time does not appear to work well among those with severe cognitive impairment. The score is missing for the vast majority of participants with CDR stage 3, and for those who do return a score it is often at the maximum allowed time for both trails; hence the information provided by this measure is likely to be extremely limited.

Association between each outcome and starting or stopping hypnotic medication

Cognitive outcomes

The change in cognitive function with changing use of hypnotics is shown in *Appendix 4*, *Figure 33–42*. There appears to be little association between Z-drug use and cognitive function, as measured by any cognitive outcome. Those who use antipsychotics and BZDs have lower cognitive function than those who do not, and starting both antipsychotics and BZDs appears to be linked to more decline across waves. When accounting for prior use of medication, neuropsychiatric symptoms and cognition these patterns remain.

Table 20 quantifies the association between change in cognitive outcomes and patterns of hypnotic use, adjusting for age, baseline cognitive function and the visit number. Those starting BZDs or antipsychotics have an associated decline in cognitive function across all measures, except delta trail time. Stopping antipsychotics is associated with improvements in CDR-SOB and animal fluency compared with those who did not use antipsychotics, but not in MMSE or delta trail time, but there is no significant improvement associated with stopping BZDs.

Those who continue Z-drugs or BZDs appear to have better cognitive function than those who did not use Z-drugs or BZDs at all.

TABLE 20 Association between change in cognitive outcomes and change in medication status between visits

	β (95% CI)			
Medication	**CDR-SOB**	**MMSE**	**Animal fluency**	**Delta trail time**
Z-drug				
No use	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
Starting	0.06 (–0.36 to 0.48)	0.34 (–0.26 to 0.93)	0.21 (–0.41 to 0.83)	–4.69 (–20.96 to 11.58)
Stopping	–0.03 (–0.38 to 0.33)	0.35 (–0.44 to 1.15)	0.56 (–0.11 to 1.22)	–11.56 (–25.68 to 2.56)
Continuing	–0.64*** (–0.95 to –0.34)	0.45 (–0.28 to 1.19)	0.65* (0.13 to 1.17)	0.31 (–11.66 to 12.29)
BZD				
No use	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
Starting	1.01*** (0.78 to 1.23)	–1.24*** (–1.71 to –0.78)	–0.49* (–0.88 to –0.10)	–3.29 (–14.11 to 7.53)
Stopping	0.02 (–0.21 to 0.26)	0.11 (–0.44 to 0.65)	0.07 (–0.37 to 0.51)	–4.11 (–14.58 to 6.35)
Continuing	–0.39*** (–0.53 to –0.24)	0.67*** (0.34 to 0.99)	0.48*** (0.23 to 0.72)	–2.19 (–7.70 to 3.31)
Antipsychotic				
No use	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
Starting	1.58*** (1.39 to 1.76)	–2.02*** (–2.41 to –1.62)	–0.94*** (–1.29 to –0.60)	1.49 (–8.09 to 11.06)
Stopping	–0.26* (–0.49 to –0.02)	–0.24 (–0.86 to 0.38)	0.74** (0.25 to 1.23)	–12.34 (–25.88 to 1.20)
Continuing	–0.10 (–0.22 to 0.02)	0.06 (–0.23 to 0.35)	0.11 (–0.13 to 0.35)	–9.27** (–14.94 to –3.61)

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
Ref, reference.

This pattern of effects is confirmed using the marginal structural model approach (see *Appendix 4*, *Table 51*), whereby use of BZDs and antipsychotics is associated with significantly worse cognition after weighting to balance users and non-users across previous CDR, previous medication use and previous levels of neuropsychiatric symptoms. There is no evidence for any effect of Z-drugs on cognitive outcomes.

Neuropsychiatric outcomes

Despite the strong association between sleep disturbance and subsequent Z-drug use, there is little association between starting Z-drugs and change in sleep disturbance between waves (*Table 21*). There is a borderline significant increase in agitation associated with starting Z-drugs and some evidence for less sleep disturbance association with stopping Z-drugs.

Similar patterns are seen for reports of anxiety and agitation, whereby those starting, stopping or continuing any of Z-drugs, BZDs or antipsychotics have higher symptom levels that those who do not use the medication at all, with a slight decline in symptoms associated with stopping medications and a significant association between medication use and symptoms remaining once prior levels of cognitive function, medication use and symptoms are taken into account.

TABLE 21 Association between mean difference in neuropsychiatric outcomes (as measured by the NPI) and change in medication status between visits

	NPI score, β (95% CI)			
Medication	Sleep	Agitation	Anxiety	Total (excluding sleep)
Z-drug				
No use	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
Starting	0.06 (–0.11 to 0.23)	0.18* (0.04 to 0.32)	0.09 (–0.04 to 0.23)	0.17 (–0.53 to 0.87)
Stopping	–0.12 (–0.26 to 0.02)	–0.06 (–0.19 to 0.06)	–0.07 (–0.20 to 0.06)	–0.41 (–0.98 to 0.16)
Continuing	–0.01 (–0.12 to 0.11)	0.03 (–0.08 to 0.14)	0.01 (–0.10 to 0.12)	0.13 (–0.33 to 0.59)
BZD				
No use	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
Starting	0.04 (–0.05 to 0.12)	0.10* (0.02 to 0.19)	0.10* (0.02 to 0.17)	0.55** (0.18 to 0.93)
Stopping	–0.11* (–0.20 to –0.02)	–0.11* (–0.20 to –0.02)	–0.15*** (–0.24 to –0.06)	–0.97*** (–1.38 to –0.56)
Continuing	–0.05* (–0.10 to –0.00)	–0.04 (–0.09 to 0.01)	–0.07** (–0.12 to –0.02)	–0.33** (–0.55 to –0.11)
Antipsychotic				
No use	0 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
Starting	0.11** (0.04 to 0.18)	0.16*** (0.09 to 0.23)	0.004 (–0.06 to 0.07)	0.77*** (0.45 to 1.09)
Stopping	–0.10 (–0.19 to 0.00)	–0.18*** (–0.28 to –0.08)	–0.22*** (–0.31 to –0.13)	–1.05*** (–1.50 to –0.59)
Continuing	–0.05* (–0.09 to –0.01)	–0.12*** (–0.16 to –0.08)	–0.10*** (–0.14 to –0.06)	–0.85*** (–1.05 to –0.64)

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
Ref, reference.

Depression and disability

As in the REDIC study, the disability measure among people with dementia is closely correlated with cognitive function, and the patterns of associations with medication use match the associations between medication use and cognitive measures.

The GDS does not appear to be linked to severity of impairment, and there is no evidence of any association between changes in depressive status and changes in use of Z-drugs, antipsychotics or BZDs (*Table 22*).

Fixed-effects models

Each of the results discussed above using marginal structural models is also reflected in the fixed-effects models (see *Appendix 4*, *Tables 52–54*). There is a strong, consistent association seen between worse cognitive function and greater disability with concurrent BZD and antipsychotic use, but no association with Z-drug use. Depression is not linked to the use of any hypnotics, except for a positive association with antipsychotics among those with no hypnotic use on study entry, whereas other neuropsychiatric symptoms are consistently positively associated with use of hypnotics, as above.

The WHELD trial results

Participant characteristics

After excluding 21 participants with missing medication data and 24 participants with a severe mental illness diagnosis, the 926 participants in the WHELD trial with dementia were mainly women ($n = 659$, 71%) and the mean age at study entry was 85.3 (SD 8.8) years. A total of 123 (13%) participants reported Z-drug use at baseline and a further 27 (3%) participants reported Z-drug use at 9-month follow-up. Those participants taking Z-drugs were more likely to have a partner, have a nervous system illness and be taking concurrent BZDs, memantine or antipsychotics (*Table 23).*

TABLE 22 Association between mean difference in depression and disability outcomes and change in medication status between visits

	β (95% CI)	
Medication status	**GDS**	**Disability**
Z-drugs		
No use	0 (Ref)	0 (Ref)
Starting	–0.28 (–0.68 to 0.13)	–0.55 (–1.23 to 0.13)
Stopping	–0.08 (–0.52 to 0.37)	–0.61 (–1.30 to 0.09)
Continuing	–0.01 (–0.31 to 0.29)	–0.65* (–1.29 to –0.01)
BZDs		
No use	0 (Ref)	0 (Ref)
Starting	0.05 (–0.21 to 0.30)	0.48** (0.14 to 0.83)
Stopping	–0.24 (–0.52 to 0.04)	–0.15 (–0.59 to 0.30)
Continuing	–0.07 (–0.24 to 0.10)	–0.64*** (–0.90 to –0.38)
Antipsychotics		
No use	0 (Ref)	0 (Ref)
Starting	0.15 (–0.07 to 0.37)	0.81*** (0.51 to 1.11)
Stopping	–0.11 (–0.52 to 0.31)	–1.24*** (–1.59 to –0.88)
Continuing	–0.02 (–0.19 to 0.15)	–1.48*** (–1.65 to –1.31)

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
Ref, reference.

TABLE 23 Participant characteristics, by Z-drug use at baseline

Baseline characteristic	Z-drug (*N* = 123)	No Z-drug (*N* = 803)
Female, *n* (%)	74 (60)	585 (73)
Age (years), mean (SD)	83.9 (9.6)	85.6 (8.6)
White ethnicity, *n* (%)	116 (94)	761 (95)
Marital status, *n* (%)[a]		
Single/widowed	71 (58)	578 (72)
Married/partner	42 (34)	162 (20)
Divorced/separated	8 (7)	54 (7)
CDR, *n* (%)		
Mild dementia	17 (14)	174 (22)
Moderate dementia	45 (37)	294 (937)
Severe dementia	61 (50)	335 (42)
NPI-NH score (excluding sleep), median (IQR)	17 (7–34)	9 (3–20)
Any sleep disturbance, *n* (%)	34 (28)	162 (20)
Pain, *n* (%)		
Mild	34 (28)	232 (29)
Moderate/severe	13 (11)	48 (6)
Comorbidity, *n* (%)		
Depression	12 (10)	99 (12)
Anxiety	4 (3)	29 (4)
Respiratory illness	42 (34)	271 (34)
Gastrointestinal illness	34 (28)	209 (26)
Cardiovascular condition	24 (20)	129 (16)
Endocrine illness	18 (15)	97 (12)
Musculoskeletal disorder	29 (24)	169 (21)
Nervous system illness	15 (12)	43 (5)
Medication use, *n* (%)		
BZD	31 (25)	98 (12)
Meprobamate/buspirone	2 (2)	7 (1)
Clomethiazole	1 (1)	11 (1)
Antidepressant	56 (46)	357 (45)
Antipsychotic	36 (29)	106 (13)
Cholinesterase inhibitor	30 (24)	170 (21)
Memantine	34 (28)	68 (9)

a Missing marital status for two participants taking Z-drugs and nine participants not taking Z-drugs.

Cross-sectional analysis

The results of the cross-sectional analyses comparing Z-drug use at baseline and baseline QoL and sleep scores are shown in *Table 24*.

At baseline, the mean QUALID scores for those taking Z-drugs or not at baseline were 22.9 (SD 8.0) and 21.3 (SD 7.3), respectively. Z-drug use was not associated with any difference in QUALID scores at baseline (RR 0.96, 95% CI 0.92 to 1.01, adjusted for confounders).

At baseline, the mean NPI-NH sleep scores for those taking Z-drugs or not at baseline were 1.6 (SD 3.0) and 1.0 (SD 2.5), respectively. There was no significant difference in sleep disturbance at baseline in Z-drug users (RR 1.42, 95% CI 0.71 to 2.85, adjusted for confounders).

At baseline, the mean NPI-NH score (excluding sleep) for those taking Z-drugs and not taking Z-drugs at baseline were 21.6 (SD 17.6) and 14.1 (SD 15.1). Greater neuropsychiatric symptoms were reported in those taking Z-drugs after adjusting for confounders (RR 1.24, 95% CI 1.00 to 1.54).

Mortality analysis

A total of 20 (16%) and 177 (22%) participants taking and not taking Z-drugs, respectively, at baseline died during follow-up. Baseline Z-drug use was not associated with mortality after adjusting for confounders (OR 0.66, 95% CI 0.38 to 1.15).

Longitudinal analyses

A total of 627 people living with dementia completed the 9-month follow-up interviews. The mean increase in QUALID, NPI-NH sleep score and NPI-NH excluding sleep over the 9 months' follow-up was 0.25 (SD 7.67), 0.11 (SD 0.60) and 0.17 (SD 16.59), respectively. Z-drug use at baseline was not significantly associated with any greater increase in either score, with adjusted additional average increases in QUALID, NPI-NH sleep, and NPI-NH excluding sleep scores of 1.43 (95% CI –0.33 to 3.19), 0.08 (95% CI –0.07 to 0.22) and 0.60 (95% CI –3.26 to 4.46), respectively (*Table 25*).

Considering changes in medication use between baseline and 9-month follow-up, 26 (4%) reported Z-drug use at baseline but not at 9 months ('stopping'), 62 (10%) participants reported Z-drug use at both times ('continuing') and 25 (4%) reported Z-drug use at 9 months but not at baseline ('starting'). Although those starting, stopping and continuing Z-drugs reported, on average, increased NPI sleep scores over the 9-month follow-up, none were statistically different from the increase for those not using Z-drugs (see *Appendix 6, Table 65*). Although those initiating Z-drugs saw a decline in their NPI score (excluding sleep), this was not statistically different from those not using Z-drugs. Although those stopping Z-drugs reported a worsening in their QoL over the 9-month follow-up, this was not statistically different from those not using Z-drugs.

TABLE 24 Adjusted IRRs for QUALID and NPI-NH sleep score, by Z-drug use at baseline

	Baseline				
Scale	Z-drug	*n*	Mean (SD)	IRR (95% CI)	IRR[a] (95% CI)
NPI-NH excluding sleep	No	803	14.1 (15.1)	1.00	1.00
	Yes	123	21.6 (17.6)	1.53 (1.23 to 1.90)	1.24 (1.00 to 1.54)
NPI-NH sleep	No	803	1.0 (2.5)	1.00	1.00
	Yes	123	1.6 (3.0)	1.57 (0.84 to 2.90)	1.42 (0.71 to 2.85)
QUALID	No	803	21.3 (7.3)	1.00	1.00
	Yes	122	22.9 (8.0)	1.07 (1.01 to 1.14)	0.96 (0.92 to 1.01)

a Adjusted for age, sex, ethnicity, marital status, CDR, Abbey Pain Scale score, comorbidity and co-medication use. QUALID scores also adjusted for sleep disturbance (a NPI-NH sleep score > 0).

TABLE 25 Adjusted additional change in QUALID, NPI-NH and NPI-NH sleep scores, by baseline Z-drug use

Scale	Baseline Z-drug	*n*	Mean change (SD)	Beta (95% CI)	Beta[a] (95% CI)
NPI-NH excluding sleep	No	539	0.33 (16.28)	0.00	0.00
	Yes	88	–0.80 (18.45)	–1.13 (–4.87 to 2.62)	0.60 (–3.26 to 4.46)
NPI-NH sleep	No	539	0.10 (0.59)	0.00	0.00
	Yes	88	0.16 (0.66)	0.06 (–0.08 to 0.19)	0.08 (–0.07 to 0.22)
QUALID	No	525	0.20 (7.42)	0.00	0.00
	Yes	85	0.52 (9.09)	0.31 (–1.45 to 2.07)	1.43 (–0.33 to 3.19)

a Adjusted for age, sex, ethnicity, marital status, baseline CDR, Abbey Pain Scale score, comorbidity and co-medication use. Change in QUALID scores also adjusted for baseline sleep disturbance (a NPI-NH sleep score > 0).

Chapter 7 Discussion

Summary of the main findings

Primary care study

By examining linked primary care and hospital admission data we found evidence of an increased risk of fractures and, in particular, hip fractures, in people with dementia taking Z-drugs. The risk also increased with cumulative exposure to Z-drugs, suggesting a causal relationship. However, multiple outcomes were examined, increasing the risk of false-positive findings. We observed a greater mortality rate in people living with dementia who were prescribed Z-drugs; however, the association did not vary significantly by cumulative exposure to Z-drugs, suggesting that this finding may be due to reverse causation (i.e. that patients in later stage dementia were more probably prescribed Z-drugs).

We did not detect a significantly increased risk of stroke, infection or venous thromboembolism with Z-drug use. We observed that people living with dementia who were prescribed Z-drugs were more likely to be further prescribed antipsychotics, antidepressants and antibiotics. People living with dementia who were prescribed Z-drugs also visited their GP more frequently and were more often admitted to hospital in the next 2 years.

Our study was not sufficiently powered to examine adverse events of BZDs, but the risk estimates for Z-drugs and fractures and mortality were generally similar to those for BZDs.

We did not find any associations between the use of low-dose TCAs and adverse events; however, these findings should be interpreted with caution, as we were unable to distinguish whether patients had been prescribed low-dose TCAs for sleep disturbance or for chronic pain. Patients with chronic or neuropathic pain may be at a lower risk of fractures than patients with sleep disturbance.

Clinical cohort studies

In cohort studies of people with dementia in Norway (the REDIC study) and the USA (the NACC data set), we observed no impact of Z-drug use on cognition, neuropsychiatric symptoms, disability or QoL. There was some suggestion of an association between recurrent Z-drug use and lesser declines in cognition and disability; however, we believe that this is more likely to reflect the people living with dementia who are stable on their Z-drugs and not progressing onto using alternative medications, such as antipsychotics or BZDs. In a cohort study of UK care home residents with dementia (the WHELD trial), we observed greater neuropsychiatric symptoms in those taking Z-drugs at baseline, but Z-drug use at baseline was not associated with greater improvement in neuropsychiatric symptoms over the following 9 months. We also observed no greater mortality risk in those taking Z-drugs.

Strengths and limitations of the study

Primary care study

The primary care study is the first study to examine a range of adverse events for Z-drug use in people with dementia. We used data from a large number of patients in a population-representative primary care database linked to hospital records, which allowed detailed analysis of the prescriptions of Z-drugs and patient-relevant outcomes. We designed the study to aim to minimise possible sources of bias and consequently this reduced the number of patients and follow-up in the study, reducing our statistical power to detect adverse events. We shall discuss the strengths and limitations in the context of the main sources of bias.[161]

Selection bias

We followed patients from their first Z-drug prescription in dementia, thus allowing for the examination of early events associated with the drug and for the evaluation of risks that may change over time.[162,163] People living with dementia already using Z-drugs when diagnosed with dementia were excluded as they may bias associations due to being 'survivors' of the early period of pharmacotherapy and having differing characteristics of persistence with their medication. We also selected a cohort of people living with dementia taking Z-drugs, but no other sedative medications, except for antipsychotics. We ceased follow-up when a new sedative medication or antipsychotic was prescribed, hence enabling greater confidence that any effects seen were attributable to the Z-drug, but this reduced statistical power. Having said that, we applied far fewer exclusion criteria than RCTs[164] and, as such, our findings are generalisable to most of the population with dementia and sleep disturbance. Our selection of patients with dementia was demonstrated to be valid, with 96% of GPs confirming the dementia diagnosis, similar to other studies using UK primary care data.[165] We are likely to have underestimated the numbers of dementia patients with sleep disturbance, but not prescribed a Z-drug, as many of these patients may not have their sleep disturbance reported to their GP. However, as our capture of dementia patients who were prescribed Z-drugs is likely to be fairly accurate, it is of less concern that we are under-representing the comparator group. In fact, those patients in the comparison group with sleep disturbance recorded by the GP are more likely to represent the more severe cases of sleep disturbance and therefore are more comparable to the group that was prescribed Z-drugs.

Validity of exposures

Although the recording of prescriptions issued in primary care may be accurate, we lack data on medications prescribed in secondary care and obtained elsewhere. However, the majority of Z-drug prescribing should be in primary care. We captured only whether or not medications were prescribed and if they were dispensed or taken. We may have underestimated the effect of Z-drug use on the adverse events, if many patients prescribed Z-drugs had not taken them. As our adverse event risks were observed only in those with repeat prescriptions of Z-drugs, these findings suggest that patients returning for further prescriptions were more likely to have taken them.

We were able to compare the risks of Z-drug use with those of BZDs. However, ensuring that the BZDs were prescribed for sleep disturbance limited the number of eligible patients and therefore our power to detect differences between BZDs and Z-drugs. As per our protocol, we also examined the medication class of low-dose TCAs; however, we advise caution in interpreting these findings as we were unable to determine the indication for these medications and sleep disturbance was confirmed in only 60% of cases in the validation study. The Z-drugs prescribed historically in the UK are zopiclone, zolpidem and zaleplon, but with zopiclone by far in the majority and zaleplon now discontinued. Although comparisons between specific Z-drugs might be of interest, there is little evidence to suggest that their effects are different and there were insufficient numbers to be able to make this comparison.

Validity of the outcomes

Patients with diagnoses recorded in the CPRD have generally been shown to have the condition.[166,167] Validity studies report around 88–100% of patients coded as having hip fracture, UTI, respiratory tract infection, venous thromboembolism and psychosis in UK primary care records databases were clinically confirmed.[166,168,169] Rates are slightly lower for stroke, where 66–76% of reported ischaemic strokes or TIAs are confirmed.[170–172] However, the degree of under-reporting in the CPRD has not often been examined. The validity of our outcomes was improved through linkage to HES and ONS. This reduced bias was due to not solely relying on the GP who probably wrote the Z-drug prescription to accurately record the outcomes. Including HES and ONS data increased our number of outcome events by approximately 46%. The number of additional events was greater in the Z-drug group than in the no sleep medication group, representing substantial bias if we had relied on the CPRD data alone (e.g. the HR for Z-drug use and fractures decreased from 1.40 to 1.27 when restricting to only the CPRD data). Other studies found that pneumonia rates increased substantially when HES linkage was included.[173]

Our recording of mortality is likely to be highly accurate as this was based on ONS records, which were also very similar to that of primary care recorded death dates. We probably underestimated forearm, wrist and hand fracture incidence, as some may have been reported to accident and emergency departments without hospital admission and may not have made it onto the primary care record. Similarly, falls are probably under-reported. GP records of falls may under-represent all falls that occur in the older population, but more accurately represent 'injurious falls requiring medical attention'.[121] However, they may be under-reported as a result of their recording being in the GP's free text, or because the medical consequence of the fall (e.g. fracture) has been recorded preferentially over the fall.

Some infections may be undetected, but we concentrated on acute bacterial ones for which medical attention would usually have been sought. We attempted to record incident behavioural and psychological symptoms of dementia by including any record of agitation, psychosis, hallucinations, delusions or aggression, but these are probably under-reported and poorly defined. They also may represent late coding of the indication for the Z-drug or BZD of interest. Hence, we express cautious interpreting of the agitation or psychosis outcome.

Although some outcomes were potentially under-reported, we do not expect substantial bias in our risk estimates due to outcome validity. Owing to the inclusion of linked HES and ONS data, we do not expect differential recording of outcomes among those prescribed Z-drugs or not. However, we examined multiple outcomes, which increased the risk of false-positive findings.

Confounding

We reduced the impact of confounding by indication by comparing adverse events to people living with dementia with recorded sleep disturbance. However, sleep disturbance was challenging to identify within the electronic primary care record. Only 42% of our control group with no sleep disturbance had sleep disturbance confirmed in our validation study. The issue of the additional pop-up screen recording the patient's sleep pattern added confusion to the often contradictory diagnosis of sleep disturbance. Discussion with health-care professionals identified a mixture of opinion that the patient has no sleep disturbance when a 'satisfactory' sleep pattern was entered, or that the GP may just want to remove the pop-up screen on sleep patterns by clicking the first option (of 'satisfactory'). We remain uncertain whether or not these patients have a sleep disturbance, but 35% and 83% of sleep disturbance was confirmed when accompanied and not accompanied, respectively, by a 'satisfactory' sleep pattern in the validation study. We performed a sensitivity analysis excluding control patients with a satisfactory sleep pattern and our effects were reduced. We are not aware of any study that has previously investigated the reliability of sleep disorder records in primary care, therefore our validation study strengthens future work on sleep disturbance using primary care data.[118]

Although the detailed primary care database allowed adjustment for a wide range of potential confounders, there is the possibility of residual confounding, the most important of which is that we were unable to measure dementia severity. Although we adjusted for duration since the dementia diagnosis, prescription of dementia medications and antipsychotics, history of agitation or psychosis and end-of-life care, there is likely to be residual confounding by dementia severity for the mortality outcome. We were also lacking information on the severity of the sleep disturbance. As more severe sleep disturbances may involve longer wandering around at night and hence greater risk of fractures, there may be residual confounding by sleep disturbance severity for the fracture outcomes. Studies have suggested that dementia severity is unrelated to fracture risk,[174] but residual confounding by stage of dementia cannot be ruled out. We also had no data on genetic information, environmental factors and cohabiting status, which have been shown to be important in falls risks in people living with dementia.[41]

Missing data

Missing data for covariates were generally low. Missing data occurring more frequently for covariates of BMI and care home, had minimal effects on the associations reported in the sensitivity analyses.

Clinical cohort studies

Generally, there were few studies reporting the outcomes of interest with sufficient Z-drug use in people living with dementia. However, the three included cohort studies were of a large size, with frequent follow-up and detailed outcome recording. Our results varied, and this could reflect differences in the prescribing of Z-drugs across the USA, UK and Norway, and the settings of nursing homes or the community. We were limited by not having a record of the outcome measurements just before the Z-drug was first prescribed. As each study measured outcomes at fixed intervals, this did not necessarily coincide with the initiation of Z-drugs or the start of a sleep disturbance. We were limited by which outcome measures each study recorded. With NPI, it is not obvious whether a respondent is reporting on the level of symptoms that are currently experienced given current treatment, or those that they believe would be experienced if the patient was not treated. Hence, these findings should be interpreted with caution.

Although in the REDIC study and the NACC data set our analysis was strengthened by using marginal structural models to balance users and non-users on prior covariates, the extent of balance was not always perfect and could not be improved using different models for estimating weights. However, balance was very good for prior CDR, suggesting that our findings are not driven by underlying differences in dementia severity. Perhaps more importantly, this approach is valid for causal inference only if the assumption of exchangeability is met, that is after balancing over the covariates included in our model there is no longer any indirect path from the exposure in question to the outcome measure.[175] In our case it is difficult to be certain of this and, as the exact timing of medication initiation is not known, it is impossible to know whether the outcome preceded each exposure or vice versa.

Interpretation of the study in light of previous research

Fractures

In the primary care study, we found evidence of a 40% greater risk of fractures with Z-drug use in people living with dementia, which is lower than that reported in studies in the older population. A systematic review, including a subgroup analysis of the findings from five observational studies in the older population, estimated a pooled relative risk for fractures of 1.73 (95% CI 1.31 to 2.27) with zolpidem use.[176] However, none of these studies accounted for sleep disturbance, which is the indication for zolpidem. A further systematic review and meta-analysis investigated Z-drugs in general and risks for falls and fractures from 14 eligible observational studies.[60] They estimated an OR of 1.70 (95% CI 1.36 to 2.12) for Z-drugs and fractures in the older population, but noted substantial heterogeneity.[60]

Although several studies have examined the risk of fractures associated with Z-drug use in the older population, studies targeting people living with dementia have been limited.[36] A recent Cochrane systematic review concluded a distinct lack of evidence to help guide drug treatment of sleep problems in dementia,[36] despite being widely prescribed to this large patient group.[177] To our knowledge, no studies have previously examined the risk of general fractures specifically in people living with dementia taking Z-drugs.

Current BZD use was not found to be associated with fractures in a study of 8036 people living with dementia in London.[41] We observed similar rates of fractures among new BZD and new Z-drug use. Other studies in the older population that compare BZDs with Z-drugs for fracture risk, report varying results, often dependent on the type of BZD.[59,178]

We found evidence of a 59% greater risk of hip fractures with Z-drug use in people living with dementia. A systematic review and meta-analysis pooled the findings from six observational studies in older adults and estimated a 90% (95% CI 68% to 113%) greater risk of hip fracture with Z-drug use.[61] However, studies suggest that the risk is lower in people living with dementia.[57,179] A Finnish study of 67,072 community-dwelling people diagnosed with Alzheimer's disease reported no association between any history of BZD or Z-drug use in the 5 years before study entry and incident hip fracture (HR 1.03, 95% CI 0.97 to 1.09); however, this exposure definition may not be sufficiently specific and would not necessarily cover

medication use immediately prior to most of the incident hip fractures (i.e. was measured only at baseline and not updated during follow-up).[179] A study of 15,528 US nursing home residents estimated an OR for non-BZD hypnotic drug use and hip fracture in residents with moderate to severe cognitive impairment of 1.43 (95% CI 1.15 to 1.77), which was lower than in the residents with no or MCI (OR 1.86, 95% CI 1.56 to 2.21).[57]

We observed that hip fracture risk increased with greater cumulative Z-drug exposure, but then tapered after 56 DDDs. This is consistent with an initial expression then down-regulation of GABA receptors,[180,181] or a depletion of susceptible patients among long-term users.[182] Other studies in the older population found similar findings, but with risks tapering over shorter periods, than we did in dementia.[59,183] This perhaps represents delays getting the prescription dispensed or many people living with dementia not taking their prescribed Z-drugs during the first month in our sample, or a slower effect of Z-drugs in dementia. We found no effect in the first 14 days, contrary to other studies in the older population.[54,56,57] This could be partly explained if some patients receiving only one prescription did not take the Z-drugs. Excluding those with only one Z-drug prescription had little effect on our cumulative Z-drug prescription findings (results available from the authors).

We observed evidence of a greater risk of hip fractures for those prescribed BZDs than Z-drugs, but numbers of hip fractures were small and this could represent residual confounding by dementia severity. Studies differ on whether they find those prescribed BZDs or Z-drugs at greater risk of hip fracture,[55,56,58,184] but generally suggest greater risks with long-acting BZDs than with Z-drugs.[56,185]

Evidence is lacking to indicate that Z-drugs increase the risk of osteoporosis,[186] in contrast to other psychotropic drugs (e.g. antidepressants and antipsychotics).[187] Although studies suggest that long-term sleep disturbance may increase osteoporosis risk though disrupting the rhythm of bone turnover.[188,189] The mechanism by which Z-drugs increase fracture risk is probably due to their effects on gait and balance, although this is contradictory to our findings on falls outcomes (see *Falls*).[59,186] A trial randomised 25 adults to 5-mg zolpidem or placebo 10 minutes before scheduled sleep and asked them to perform 10 tandem walks on a beam on night-time awakening.[190] The NNH was estimated as one tandem walk failure for every 1.7 (95% CI 1.4 to 2.0) older adults treated with zolpidem. The trial authors concluded that the 'use of nonbenzodiazepine hypnotic medications may have greater consequences for health and safety than previously recognized'.[190]

In a comprehensive review of the evidence for major adverse outcomes of BZDs and Z-drugs, there was compelling evidence to establish a causal connection between BZD or Z-drug use and only motor vehicle accidents, falls and fractures.[186] Our study suggests that the increased risk of fractures extends to those people living with dementia taking Z-drugs.

Falls

Counterintuitive to the fractures findings in the primary care study, we did not find an increased falls risk with Z-drug use. Similarly, current BZD use was also not found to be associated with falls in a study of 8036 people living with dementia in London, once accounting for differences in ethnicity, living environment and disability.[41] A systematic review published in 2008, reported modest associations (RRs 1.2–1.3) between BZDs and falls in nursing home residents with dementia,[191] and BZDs are consistently associated with around a 20% increased falls risk in older people.[48]

Z-drugs were originally claimed to cause fewer falls,[51] but a recent meta-analysis estimated an OR for Z-drug use and falls of 2.40 (95% CI 0.92 to 6.27) when pooling the findings from three observational studies in adult populations.[60] However, there was considerable heterogeneity (97%) between the studies and reasons for this were cited as difficulty recording falls, particularly in patients with multimorbidity, or recall bias in the studies relying on self-reported falls. Among 4450 US community-dwelling older men enrolled in the Osteoporotic Fractures in Men study, Z-drug use was associated with a 37% (95 CI 9% to 71%) greater risk of a self-reported fall.[192]

Falls are thought be the main mechanism whereby increased fractures and injury occur in Z-drug users resulting from the sedation effect. Falls also account for 90% of hip fractures.[193] A study of older people in Taiwan found that high doses of Z-drugs were associated with an increased risk of fall-related injuries requiring hospitalisation (OR 1.24, 95% CI 1.05 to 1.48), so the lack of association between Z-drug use and falls in our study might be considered surprising.[53]

To gain a potential clinical explanation we discussed this finding with our health-care advisory panel, who suggested that a fracture would be coded in electronic records preferentially over falls as the cause for their referral or reason for admission to hospital. This does suggest that in such cases, if a fracture is a direct result of a fall, it could be missed in our analysis due to our reliance on the complete recording of all required coding during contact with a GP or hospital. Alternatively, although the rate of falls may have been similar between groups, it is possible that the nature of the falls may have been more severe or of greater physical impact in patients taking Z-drugs.

Mortality

We observed a 34% increased mortality rate in people living with dementia prescribed Z-drugs, using primary care data; however, no association in UK nursing homes (the WHELD trial). Other studies have been conflicting on the effect of hypnotic use on mortality. A study of 31,140 community-dwelling people with Alzheimer's disease in Finland, found that BZD use was associated with increased risk of mortality (HR 1.59, 95% CI 1.35 to 1.88), but not Z-drug use (HR 1.06, 95% CI 0.83 to 1.35), after accounting for psychotropic drug use, comorbidities, socioeconomic status, hip fractures and stroke.[75] In a US study,[74] crude mortality rates were higher in people living with dementia taking hypnotics, but the association was not tested statistically.

A systematic review and meta-analysis examining the effect of hypnotics on mortality estimated a HR of 1.73 (95% CI 0.95 to 3.16) when pooling the findings from five observational studies on Z-drug use and mortality risk in adults.[71] However, there was considerable heterogeneity (I^2 = 97%), with three studies reporting no effect and two with HRs > 3. Two of these studies used similar UK primary data to our study. One matched 2435 Z-drug initiators to two non-initiators on age, sex and general practice in the UK adult population during 1998–2001, and reported a HR for mortality of 3.32 (95% CI 3.19 to 3.45), adjusted for age, sex, comorbidities and co-medications, with a fairly constant risk across cumulative Z-drug prescriptions, similar to our study.[194] A further study of 4964 UK patients with pneumonia showed that patients were not at a greater mortality risk if taking zopiclone (HR 1.11, 95% CI 0.77 to 1.60).[64] Studies on Z-drug or BZD use and mortality have been conflicting,[64,70–72,194] and reported associations may simply stem from confounding.[73] A large database study of US adults observed an increased mortality rate in 1.25 million BZD initiators matched to 1.25 million patients not initiating BZDs, but not once accounting for comorbidities, concomitant medications and health-care utilisation via propensity score matching (HR 0.89, 95% CI 0.85 to 0.94 in those aged > 65 years).[195]

We found the same risk of mortality regardless of cumulative Z-drug exposure from our dose–response analysis, suggesting that the relationship may not be causal between Z-drug use and mortality risk in this case. We suspect that our findings are at least partially due to residual confounding by indication, whereby the cohort of patients on Z-drugs are already at increased risk of death.[73] However, it could also be speculated that the increased risk of hip fractures in this group drives an increased mortality rate, given that older adults have a five- to eightfold increased risk for all-cause mortality during the first 3 months after a hip fracture.[196]

Infections

In the primary care study we did not find a statistically significant increased risk of infections in Z-drug users (HR 1.10, 95% CI 0.92 to 1.32 for UTI and LRTI). However, there was a suggestion of an increased infection risk after 28 DDDs of Z-drugs were prescribed, and we observed a greater rate of antibiotic prescribing. A Finnish study of community-dwelling adults with Alzheimer's disease found that BZD use was associated with increased pneumonia rates and also found a very similar Z-drug use estimate to our study (HR 1.10, 95% CI 0.84 to 1.44).[67]

A meta-analysis pooled data from published or Food and Drug Administration RCTs on 2432 participants randomised to eszopiclone and on 1626 participants randomised to zolpidem, estimated RRs of 1.48 (95% CI 1.25 to 1.74) and 1.99 (95% CI 1.21 to 3.26) for infections, respectively.[63] Observational studies in the adult population vary according to whether or not they detect an increased risk of infection with Z-drug use. A UK study using similar primary care to our study did not detect a significant association between Z-drug prescription and influenza-like illness-related pneumonia (HR 1.18, 95% CI 0.89 to 1.56).[66] A study in Taiwan found that patients using zolpidem with cumulative DDDs of 1–28, 29–84 and > 84 had HRs of 1.67 (95% CI 1.32 to 2.11), 1.91 (95% CI 1.47 to 2.49) and 1.62 (95% CI 1.32 to 1.98), respectively, compared with patients who did not use zolpidem during a 3-year follow-up.[65] However, there is probably residual confounding due to accounting only for a comorbidity score and few co-medications. A later case–control study in Taiwan in adults with chronic kidney disease found no difference in Z-drug use at the time of pneumonia (OR 1.07, 95% CI 0.80 to 1.44).[197]

The mechanism whereby Z-drug use may increase infection is uncertain. It has been speculated that BZDs may suppress immune surveillance, which is supported by animal study findings.[63] Alternatively, Z-drugs could impair the clearing of oral secretions through inhibiting the swallowing of saliva.[68] Another possibility is that Z-drugs may increase gastro-oesophageal reflux events during sleep by relaxing the lower oesophageal sphincter.[198]

Our study and the supporting literature suggest that if there is a greater risk of acute infections with Z-drug use in people living with dementia, then it is likely to be small and our study was inadequately powered to detect it.

Cardiovascular outcomes

In the primary care study we did not find a statistically significant increased risk of ischaemic stroke (HR 1.33, 95% CI 0.85 to 2.07) or venous thromboembolism (HR 1.66, 95% CI 0.69 to 3.98) to people living with dementia prescribed Z-drugs. However, there was a suggestion of an increased stroke risk after 28 DDDs of Z-drugs were prescribed. A study of 45,050 community-dwelling persons with Alzheimer's disease in Finland reported that BZD or Z-drug prescription was associated with a 21% (95% CI 4% to 40%) increased risk of stroke, and this risk did not vary when stratified by BZD or Z-drug use.[77] However, residual confounding is possible as they were unable to account for sleep disturbance or dementia severity. A case–control study of adults in Taiwan found that exposure to zolpidem was associated with increased risks of ischaemic stroke (OR 1.37, 95% CI 1.30 to 1.44), increasing further with greater exposure to zolpidem.[78] They also found that regardless of whether or not a person presented with a sleep disorder, the risk of stroke was increased with zolpidem use (OR 1.37 without a sleep disorder and 1.41 with a sleep disorder), suggesting that the increased risk was due to drug use and not the sleep disturbance itself.

Mechanisms for Z-drugs causing increased stroke risk are uncertain, but speculated to relate to a decrease in local cerebral blood flow.[77] However, there is evidence that sleep disturbances increase stroke risk,[199] suggesting that residual confounding by indication could underlie reported associations. We are not aware of any studies examining Z-drug use and risk of venous thromboembolism, although sleep disturbance has been observed to be a risk factor.[200]

Prescriptions and health-care utilisation

In the primary care study, we found that people living with dementia who were prescribed Z-drugs were more likely to be initiated on antipsychotics and antidepressants. In line with our findings, a study in Taiwan reported that Z-drug users aged > 65 years were more frequently exposed to antipsychotics (OR 1.31, 95% CI 1.14 to 1.50), antidepressants (OR 1.45, 95% CI 1.28 to 1.65) and opioids (OR 2.38, 95% CI 2.07 to 2.73).[53] We also found that people living with dementia who were prescribed Z-drugs had more GP and hospital visits. This could reflect the increased risk of fractures in these patients, which would drive increased service use. The study in Taiwan also found that older adults who were prescribed Z-drugs were at an increased risk of fall-related injuries necessitating hospitalisation (OR 1.24, 95% CI 1.05 to 1.48).[53]

Cognition, quality of life and sleep disturbance

In the clinical cohort studies, we found no evidence that Z-drug use impacts significantly on cognitive function or QoL. This differs from other studies in older adults with insomnia, which reported that hypnotic use is associated with reduced HRQoL.[101,102] Greater cognitive declines have been reported in people living with dementia taking BZDs;[96] however, to the best of our knowledge, no other studies have examined the impact of Z-drugs on cognition in people living with dementia.

Estimating the effect of Z-drug use on sleep disturbance was challenging using the observational data sets, given that sleep scores were not measured immediately prior to Z-drug initiation; however, we observed no impact of Z-drug use on sleep scores. This is in line with other studies, suggesting that the use of sedating hypnotics in the general population does not improve sleep, human performance or general health, calling into doubt their effectiveness.[103,104]

Chapter 8 Conclusions

The evidence suggests an increased risk of fractures in people living with dementia and taking Z-drugs, which is cause for concern. However, our study is limited by being observational with possible residual confounding and the many outcomes examined increases the chances of false-positive findings. In the past, Z-drugs have been thought of as a safer alternative to BZDs for the management of sleep disturbance, and their usage has been increasing with drives to decrease antipsychotic and BZD prescribing.[110] One meta-analysis reported a pooled estimate of a 92% increased risk of fractures with zolpidem use (RR 1.92, 95% CI 1.65 to 2.24),[176] exceeding the risk reported with BZD use in some studies.[55,58] Another meta-analysis similarly found that Z-drugs were associated with higher risk of hip fracture (RR 1.90, 95% CI 1.68 to 2.13) than BZD use (RR 1.52, 95% CI 1.37 to 1.68).[61] The evidence suggests that Z-drugs may not be a safer alternative to BZDs, particularly in the context of fractures, and that they may need to be used with similar caution.

Furthermore, previous studies have mostly targeted the older population, whereas our study specifically focuses the use of Z-drugs in people living with dementia, for whom fracture rate risk is already higher, particularly hip fractures.[201,202] There has previously been little evidence of the specific effects in people living with dementia; our study has provided targeted information for this vulnerable and growing patient group, which will be valuable to both patients and carers but also health-care professionals.[62]

Clinical implications

It is important to remember that the population with dementia who are taking Z-drugs is likely to include people with more severe dementia than the population taking no medication for sleep disturbance, so we cannot assume that the effects we observe are entirely causal. With that in mind, we estimate that the absolute annual risks of fractures and hip fractures in the unexposed group are 7.4% and 3.2%, respectively. These equate to annual risks of 10.2% and 5.0% for fractures and hip fractures, respectively, when taking Z-drugs. If causal, this is equivalent to 36 and 56 people living with dementia being treated with Z-drugs before a fracture or hip fracture occurs, respectively.

The consequences of hip fracture are particularly serious for older people with dementia. In the UK in 2011 hip fracture cases cost around £1B per year,[203] with UK hospital costs alone estimated to be £14,163 and £2139 in the first and second year following hip fracture in 2012–13.[204] In England, 648,465 people have dementia, of whom 436,416 (67.3%) are diagnosed.[205] Using an estimate of the prevalence of Z-drug use in people living with dementia in Scotland of 9% in 2011, assumes 39,277 people diagnosed with dementia are taking Z-drugs per year.[206] The additional annual hospital cost to the NHS of hip fractures for people with a diagnosis of dementia who take Z-drugs is likely to be in the order of £11.5M, assuming £16,302 per hip fracture for the additional 1.8% of the exposed population. The wider NHS and societal costs are likely to be much higher.

The individual decision to prescribe a sleep drug includes balancing many complex and often competing risks and benefits for patients and carers. Our estimated increased risks for fractures were also comparatively small for the individual patient, so patients would need to be reviewed on a case-by-case basis to assess whether or not their risks outweigh their individual potential benefits from Z-drugs. Further research is also required to confirm whether or not an increased risk of fractures, hip fracture and potentially mortality should be considered when prescribing Z-drugs. Our findings suggest that when pharmacological management of sleep disturbance is initiated, fracture risk management plans may need to be implemented and monitored to mitigate potential adverse health outcomes.

Implications for further research

Further research is needed to confirm our findings of an increased fracture risk with Z-drug use in people living with dementia. Research is needed to better understand whether or not Z-drugs increase the risk of falls, and to understand the mechanism and type of falls, for example if the risk varies by time of day (e.g. is it through drowsiness on waking in the morning, or falls from bed or getting to the bathroom at night). In addition, studies should examine whether or not Z-drugs contribute by any other mechanism to increase fracture risk (e.g. via increasing the risk of osteoporosis). Although further well-designed observational studies may provide additional evidence, RCTs are needed to obtain a clear assessment of potential risks. A pragmatic cluster trial that includes de-prescribing of Z-drugs as part of a multifaceted intervention, delivered in community settings, would be feasible and could include detailed falls reporting. Our findings suggest that ideally patients should be de-prescribed Z-drugs soon after starting them, to avoid them developing tolerance to the Z-drugs. Such trials should also consider the informal carer burden associated with any intervention, as this is often overlooked.[207]

Our study highlights the lack of existing studies that routinely record outcome information on the carer(s) of people living with dementia. It was an aim in our original protocol to examine carer outcomes, but we found very few sufficiently large studies that recorded them. In balancing the risks and benefits of treatments for sleep disturbance, information on any potential benefits to carers is a key piece in the decision-making that we are missing. Other research has suggested that informal carers, in general, find medication management for people living with dementia challenging.[208] Particular challenges include monitoring for adverse events and deciding whether or not to administer an 'as required' medication, such as a hypnotic. More research is needed on carer outcomes to properly be able to weigh up the risks and benefits of Z-drugs in people living with dementia.

Further research is needed into alternative non-pharmacological therapies and whether or not they may be appropriate as first-line treatments for sleep disturbance in dementia.[209] Various studies have examined artificial light therapy for people living with dementia, but a recent Cochrane review concluded they had no effect on sleep activity.[210] Further studies should pursue activity programmes that include outdoor light, as some have demonstrated positive benefits on sleep. A daily structured activity programme offered outdoors was successful in increasing sleep duration in nursing home residents with dementia.[211] In addition, a multidimensional intervention including sunlight exposure, increased activities and improved sleep hygiene was successful in reducing daytime napping and decreased night-time awakenings in care home residents.[212] Programmes with individualised social activities have demonstrated improved sleep outcomes in people living with dementia, whereas other interventions have had mixed findings.[213] However, the previous studies have been criticised for their inconsistency and for not building on each other.[213] Replication is needed in order to be more confident about the evidence base. Previous studies have also highlighted the need for a personalised approach to sleep disturbance interventions.[213] Research into multicomponent personalised therapies that combine light therapy and activity components may be fruitful.[214] In addition, more research is needed to better understand the differing types of sleep disturbance in dementia and their underlying mechanisms in order to better target possible treatments.[215,216]

This study highlights important issues for sleep disturbance research, using UK patient electronic medical records. To our knowledge, no previous studies have investigated the validity of sleep disturbance coding in UK primary care data. However, our validation study identified that only 55% of people living with dementia coded with a diagnosis or symptom of sleep disturbance had this diagnosis confirmed by their GP, highlighting some anomalies. We also found that sleep disturbance diagnoses were unlikely to occur within the primary care Read codes. For example, Z-drugs are prescribed exclusively for sleep disturbance, but only 18% of people living with dementia prescribed a Z-drug had a code for sleep disturbance on the date of the Z-drug prescription. From conversations with our health-care professional panel it seems that, due to time constraints during GP appointments, often only the primary conditions are coded. It could also potentially be an issue of 'diagnostic overshadowing', whereby the fact that the patient has a diagnosis of dementia is taking priority over the recording of other relevant diagnoses.[217] This information is important for future epidemiological research relying on sleep disturbance Read coding in medical records; without free text it can be problematic to confirm or gain further insight into sleep disturbance issues in patients.

Another limitation of existing standardised primary care data sets for dementia research is that they lack information on the severity of dementia or the cognitive state of the people living with dementia. Further linkages of large primary care databases with secondary care memory clinics and dementia services would be beneficial to advance research in dementia.

We found that considerable bias would have affected our risk estimates if we had not included linkage to hospital admissions data. We recommend that research on the effects of medication using UK primary care data additionally uses linked data sets when possible.[218]

Acknowledgements

There are many who contributed to this research project; we would like to thank to following people for their valuable participation.

We are grateful to the patients who participated in the clinical trial and cohort study data sets, which we subsequently repurposed for our study.

The NACC database is funded by the National Institute on Aging/National Institutes of Health grant U01 AG016976. The NACC data are contributed by the National Institute on Aging-funded ADCs: P30 AG019610 [principal investigator (PI) Eric Reiman, Doctor of Medicine (MD)], P30 AG013846 (PI Neil Kowall, MD), P50 AG008702 (PI Scott Small, MD), P50 AG025688 [PI Allan Levey, MD, Doctor of Philosophy (PhD)], P50 AG047266 (PI Todd Golde, MD, PhD), P30 AG010133 (PI Andrew Saykin, Doctor of Psychology), P50 AG005146 (PI Marilyn Albert, PhD), P50 AG005134 (PI Bradley Hyman, MD, PhD), P50 AG016574 (PI Ronald Petersen, MD, PhD), P50 AG005138 (PI Mary Sano, PhD), P30 AG008051 (PI Thomas Wisniewski, MD), P30 AG013854 (PI M. Marsel Mesulam, MD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG010161 (PI David Bennett, MD), P50 AG047366 (PI Victor Henderson, MD, MS), P30 AG010129 (PI Charles DeCarli, MD), P50 AG016573 (PI Frank LaFerla, PhD), P50 AG005131 (PI James Brewer, MD, PhD), P50 AG023501 (PI Bruce Miller, MD), P30 AG035982 (PI Russell Swerdlow, MD), P30 AG028383 (PI Linda Van Eldik, PhD), P30 AG053760 (PI Henry Paulson, MD, PhD), P30 AG010124 (PI John Trojanowski, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005142 (PI Helena Chui, MD), P30 AG012300 (PI Roger Rosenberg, MD), P30 AG049638 (PI Suzanne Craft, PhD), P50 AG005136 (PI Thomas Grabowski, MD), P50 AG033514 (PI Sanjay Asthana, MD, Fellowship of the Royal College of Physicians of London), P50 AG005681 (PI John Morris, MD) and P50 AG047270 (PI Stephen Strittmatter, MD, PhD).

Robert Howard is supported by the University College London Hospitals NIHR Biomedical Research Centre.

We are grateful to the GPs who completed the GP questionnaires as part of the validation study and to Emma Boyle (Medicines and Healthcare products Regulatory Agency) for her support facilitating the GP questionnaire.

We also thank our PPI and health-care professional advisory group members for their valuable contributions to the ZED study, including Kate Massey, Peter Richmond, Lesley Evans, Heather Edwards, Tris Jackson, Mandi Bowhill, Amander Wellings, Rebecca Harmston, Jay Foden, Maureen Tilford, Daisy Lo, Magda Turczyn and Liz Yaxley. Kate Massey was a member of the Study Steering Committee in a PPI advisory role, as well as a member of the ZED PPI Advisory Team. Their knowledge and insights based on real-life experiences provided critical information and contribution throughout the study. We would also like to thank the PPI group co-ordinator, Rhianna Broadway (Inspire), and the HCP group co-ordinator, Sarah Housden, for their support during the study.

We thank those who provided data for the clinical cohort studies, including those that were kindly offered but we were not able to use and, in particular, to Dr Sverre Bergh (Innlandet Hospital Trust, Norway) who facilitated access to the REDIC study data.

We additionally would like to thank members of our Steering Group Committee for their support and guidance throughout the study.

Disclaimers

This study is based in part on data from the CPRD, obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this report are those of the authors alone.

Contributions of authors

Kathryn Richardson (https://orcid.org/0000-0002-0741-8413) (Research Fellow in Statistics, University of East Anglia) was a co-applicant, co-developed and co-wrote the funding application. Led the statistical design and analysis of the primary care study and the WHELD trial data set, and was responsible for writing and revising this report.

George M Savva (https://orcid.org/0000-0001-9190-124X) (Institute Statistician, Quadram Institute, formerly Senior Lecturer in Applied Statistics, University of East Anglia) was chief investigator for the study in the period June 2016–September 2017. He co-developed the study concept and led the study design and the funding application, led the statistical design and analysis for the clinical data sets of the REDIC study and NACC, and contributed to writing and revising this report.

Penelope J Boyd (https://orcid.org/0000-0003-4786-1230) (Senior Research Associate, University of East Anglia) was the research assistant from October 2017 to July 2018. She contributed to PPI and health-care professional activity, dissemination and literature review, and co-ordinated and contributed to writing and revising this report.

Clare Aldus (https://orcid.org/0000-0002-0197-2755) (Research Fellow, University of East Anglia) was study manager from October 2017 to July 2018. She managed the research and administrative team, governance, impact and dissemination, and contributed to writing and revising this report.

Ian Maidment (https://orcid.org/0000-0003-4152-9704) (Reader in Clinical Pharmacy, Aston University) was a co-applicant and pharmacy lead. He provided expertise in dementia and medication optimisation, contributed to study design and development, interpretation of the data, and contributed to writing and revising this report.

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Publication

Richardson K, Loke YK, Fox C, Maidment I, Howard R, Steel N, *et al.* Adverse effects of Z-drugs for sleep disturbance in people living with dementia: a population-based cohort study. *BMC Med* 2020;**18**:351.

Data-sharing statement

Data from the CPRD cannot be shared by the authors but are available directly from the CPRD. Full code lists corresponding to each of the covariates we included are available from the authors on request.

Data from the REDIC study are available for researchers in co-operation with the data owner, the Research Centre For Old Age Psychiatry Research – Innlandet Hospital Trust. Information is available at https://sykehuset-innlandet.no/avdelinger/alderspsykiatrisk-forskningssenter (accessed 6 December 2019).

Data from the NACC data set are available directly from the National Alzheimer's Coordinating Center on application.

Data from the WHELD trial are available by approval from the Trial Management Committee for the WHELD trial.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Coding used to identify dementia and sleep disturbance diagnosis, and outcomes in the primary care study

The dementia code list is the Quality and Outcomes Framework definition, excluding alcohol-induced dementia, and is very similar to lists other validated studies have used (*Table 26*).[165]

TABLE 26 Dementia code list

MedCode	Read code	Read term
33707	E00..00	Senile and presenile organic psychotic conditions
1916	E00..11	Senile dementia
1350	E00..12	Senile/presenile dementia
7323	E000.00	Uncomplicated senile dementia
15165	E001.00	Presenile dementia
42602	E001000	Uncomplicated presenile dementia
49513	E001100	Presenile dementia with delirium
30032	E001200	Presenile dementia with paranoia
27677	E001300	Presenile dementia with depression
38438	E001z00	Presenile dementia NOS
44674	E002.00	Senile dementia with depressive or paranoid features
18386	E002000	Senile dementia with paranoia
21887	E002100	Senile dementia with depression
41089	E002z00	Senile dementia with depressive or paranoid features NOS
37015	E003.00	Senile dementia with delirium
19477	E004.00	Arteriosclerotic dementia
8634	E004.11	Multi infarct dementia
43089	E004000	Uncomplicated arteriosclerotic dementia
56912	E004100	Arteriosclerotic dementia with delirium
55467	E004200	Arteriosclerotic dementia with paranoia
43292	E004300	Arteriosclerotic dementia with depression
42279	E004z00	Arteriosclerotic dementia NOS
15249	E00y.00	Other senile and presenile organic psychoses
51494	E00y.11	Presbyophrenic psychosis
2882	E00z.00	Senile or presenile psychoses NOS
62132	E02y100	Drug-induced dementia
25386	E041.00	Dementia in conditions EC
7664	Eu00.00	[X]Dementia in Alzheimer's disease
49263	Eu00000	[X]Dementia in Alzheimer's disease with early onset
25704	Eu00011	[X]Presenile dementia, Alzheimer's type

continued

TABLE 26 Dementia code list (*continued*)

MedCode	Read code	Read term
60059	Eu00012	[X]Primary degen dementia, Alzheimer's type, presenile onset
61528	Eu00013	[X]Alzheimer's disease type 2
38678	Eu00100	[X]Dementia in Alzheimer's disease with late onset
46762	Eu00111	[X]Alzheimer's disease type 1
11379	Eu00112	[X]Senile dementia, Alzheimer's type
43346	Eu00113	[X]Primary degen dementia of Alzheimer's type, senile onset
30706	Eu00200	[X]Dementia in Alzheimer's disease, atypical or mixed type
29386	Eu00z00	[X]Dementia in Alzheimer's disease, unspecified
8195	Eu00z11	[X]Alzheimer's dementia unspecified
6578	Eu01.00	[X]Vascular dementia
9565	Eu01.11	[X]Arteriosclerotic dementia
46488	Eu01000	[X]Vascular dementia of acute onset
11175	Eu01100	[X]Multi-infarct dementia
55838	Eu01111	[X]Predominantly cortical dementia
8934	Eu01200	[X]Subcortical vascular dementia
31016	Eu01300	[X]Mixed cortical and subcortical vascular dementia
55313	Eu01y00	[X]Other vascular dementia
19393	Eu01z00	[X]Vascular dementia, unspecified
12621	Eu02.00	[X]Dementia in other diseases classified elsewhere
28402	Eu02000	[X]Dementia in Pick's disease
54106	Eu02100	[X]Dementia in Creutzfeldt-Jakob disease
37014	Eu02200	[X]Dementia in Huntington's disease
9509	Eu02300	[X]Dementia in Parkinson's disease
26270	Eu02500	[X]Lewy body dementia
64267	Eu02y00	[X]Dementia in other specified diseases classified elsewhere
4693	Eu02z00	[X]Unspecified dementia
48501	Eu02z11	[X]Presenile dementia NOS
47619	Eu02z12	[X]Presenile psychosis NOS
34944	Eu02z13	[X]Primary degenerative dementia NOS
4357	Eu02z14	[X]Senile dementia NOS
27935	Eu02z15	[X]Senile psychosis NOS
27759	Eu02z16	[X]Senile dementia, depressed or paranoid type
53446	Eu04100	[X]Delirium superimposed on dementia
1917	F110.00	Alzheimer's disease
16797	F110000	Alzheimer's disease with early onset
32057	F110100	Alzheimer's disease with late onset
11136	F111.00	Pick's disease
29512	F112.00	Senile degeneration of brain
7572	F116.00	Lewy body disease
59122	Fyu3000	[X]Other Alzheimer's disease

EC, elsewhere classified; NOS, not otherwise specified.

Sleep disturbance

The following diagnosis and referral codes are classified according to being 'probable' or 'possible' evidence of a sleep disorder in a dementia patient (*Table 27*).

TABLE 27 Sleep disorder codes

MedCode	Read code	Read term	Possible or probable sleep disturbance
21305	1B1B.00	Cannot sleep – insomnia	Probable
4537	1B1B.11	C/O – insomnia	Probable
3523	1B1B000	Initial insomnia	Probable
5675	1B1B100	Middle insomnia	Probable
4597	1B1B200	Late insomnia	Probable
7725	1B1Q.00	Poor sleep pattern	Probable
30385	1BN1.00	Wanders at night	Probable
94508	1BN2.00	Wanders during the day and at night	Probable
42847	1BX0.00	Delayed onset of sleep	Probable
60806	1BX2.00	Sleeping pattern	Probable
60974	1BX9.00	Light sleep	Probable
96037	8G9B.00	Sleep hygiene behaviour education	Probable
95887	8HTn.00	Referral to sleep clinic	Probable
12072	8Q0..00	Sleep management	Probable
107666	9Ngt.00	On melatonin for sleep disorder	Probable
7819	E274.00	Non-organic sleep disorders	Probable
26546	E274.12	Insomnia due to nonorganic sleep disorder	Probable
15515	E274100	Transient insomnia	Probable
4023	E274111	Insomnia NOS	Probable
16115	E274200	Persistent insomnia	Probable
39990	E274B00	Repeated rapid eye movement sleep interruptions	Probable
55179	E274C00	Other sleep stage or arousal dysfunction	Probable
19514	E274D11	Restless sleep	Probable
32987	E274E00	'Short-sleeper'	Probable
36745	E274F00	Inversion of sleep rhythm	Probable
30626	Eu51000	[X]Nonorganic insomnia	Probable
23923	Eu51200	[X]Nonorganic disorder of the sleep-wake schedule	Probable
42753	Eu51211	[X]Psychogenic inversion of circadian rhythm	Probable
101729	Eu51213	[X]Psychogenic inversion of sleep rhythm	Probable
5921	Fy00.00	Disorders of initiating and maintaining sleep	Probable
8997	Fy02.00	Disorders of the sleep-wake schedule	Probable
8084	R005.00	[D]Sleep disturbances	Probable
10349	R005.11	[D]Insomnia – symptom	Probable
31236	R005.12	[D]Sleep rhythm problems	Probable

continued

TABLE 27 Sleep disorder codes (*continued*)

MedCode	Read code	Read term	Possible or probable sleep disturbance
750	R005200	[D]Insomnia NOS	Probable
16447	R005500	[D]Sleep rhythm inversion	Probable
15732	R005600	[D]Sleep rhythm irregular	Probable
58911	R005700	[D]Sleep-wake rhythm non-24-hour cycle	Probable
54458	R005800	[D]Sleep dysfunction with sleep stage disturbance	Probable
22081	Z1M..00	Sleep and rest interventions	Probable
101913	Z1M1.00	Disturbing sleep	Probable
51397	ZV1B100	[V]Personal history of unhealthy sleep-wake schedule	Probable
43397	Z7CCC00	Found wandering the streets	Possible
26009	Z7CCB00	Wandering	Possible
15407	R005z00	[D]Sleep dysfunction NOS	Possible
41737	R005900	[D]Sleep dysfunction with arousal disturbance	Possible
1244	R005000	[D]Sleep disturbance, unspecified	Possible
15283	K5A2100	Menopausal sleeplessness	Possible
53912	Fyu5800	[X]Other sleep disorders	Possible
49601	Fy05.00	Nocturnal sleep-related eating disorder	Possible
2329	Fy0..00	Sleep disorders	Possible
21032	Eu51z11	[X]Emotional sleep disorder NOS	Possible
22819	Eu51z00	[X]Nonorganic sleep disorder, unspecified	Possible
62925	Eu51y00	[X]Other nonorganic sleep disorders	Possible
17687	Eu51511	[X]Dream anxiety disorder	Possible
6943	Eu51300	[X]Sleepwalking	Possible
24894	Eu51.00	[X]Nonorganic sleep disorders	Possible
27649	E274z00	Non-organic sleep disorder NOS	Possible
8519	E274y11	Dreams	Possible
43098	E274y00	Other non-organic sleep disorder	Possible
48783	E274D00	Repetitive intrusions of sleep	Possible
47745	E274600	Shifting sleep-work schedule	Possible
7409	E274500	Jet lag syndrome	Possible
36992	E274300	Transient hypersomnia	Possible
16434	E274000	Unspecified non-organic sleep disorder	Possible
93615	9Nk0.00	Seen in sleep clinic	Possible
103449	1F9C.00	Eats at night	Possible
9090	1BN..00	Wandering	Possible
8123	1B1O.00	Restless	Possible
56809	7065800	Sleep studies	Possible
4559	3148	Sleep studies	Possible

NOS, not otherwise stated.

Exclusions: severe mental illness or Down syndrome

Patients will be excluded if they are diagnosed with a severe mental illness or Down syndrome before their dementia diagnosis (*Table 28*).

TABLE 28 Patient Read codes excluded if there is a diagnosis of severe mental illness or Down syndrome

MedCode	Read code	Read term
1543	PJ0..00	Down's syndrome – trisomy 21
10759	PJ0z.00	Down's syndrome NOS
18415	PJ0..12	Trisomy 21
23489	PJ0..11	Mongolism
32010	PJ01.00	Trisomy 21, mosaicism
42701	PJ00.00	Trisomy 21, meiotic nondisjunction
61499	PJ02.00	Trisomy 21, translocation
61627	PJ0z.11	Trisomy 21 NOS
101309	PJ02.11	Partial trisomy 21 in Down's syndrome
107919	PJ01.11	Trisomy 21, mitotic nondisjunction
15958	E1...00	Non-organic psychoses
854	E10..00	Schizophrenic disorders
32222	E100.00	Simple schizophrenia
73295	E100.11	Schizophrenia simplex
15733	E100000	Unspecified schizophrenia
3984	E100200	Chronic schizophrenic
44498	E100400	Acute exacerbation of chronic schizophrenia
58687	E100500	Schizophrenia in remission
53625	E100z00	Simple schizophrenia NOS
25546	E102.00	Catatonic schizophrenia
102427	E102500	Catatonic schizophrenia in remission
1494	E103.00	Paranoid schizophrenia
33383	E103000	Unspecified paranoid schizophrenia
31362	E103200	Chronic paranoid schizophrenia
53032	E103400	Acute exacerbation of chronic paranoid schizophrenia
36172	E103500	Paranoid schizophrenia in remission
9281	E103z00	Paranoid schizophrenia NOS
576	E104.00	Acute schizophrenic episode
96883	E105500	Latent schizophrenia in remission
38063	E106.00	Residual schizophrenia
2117	E107.00	Schizo-affective schizophrenia
58862	E107000	Unspecified schizo-affective schizophrenia
43800	E107200	Chronic schizo-affective schizophrenia
56438	E107500	Schizo-affective schizophrenia in remission
10575	E107z00	Schizo-affective schizophrenia NOS
33338	E10y000	Atypical schizophrenia

continued

TABLE 28 Patient Read codes excluded if there is a diagnosis of severe mental illness or Down syndrome (*continued*)

MedCode	Read code	Read term
49761	E10yz00	Other schizophrenia NOS
8407	E10z.00	Schizophrenia NOS
14656	E11..00	Affective psychoses
8567	E11..11	Bipolar psychoses
2560	E11..12	Depressive psychoses
26161	E11..13	Manic psychoses
37070	E110.00	Manic disorder, single episode
18909	E110.11	Hypomanic psychoses
20110	E110000	Single manic episode, unspecified
14728	E110100	Single manic episode, mild
70000	E110600	Single manic episode in full remission
36611	E110z00	Manic disorder, single episode NOS
26227	E111.00	Recurrent manic episodes
19967	E111000	Recurrent manic episodes, unspecified
32295	E111400	Recurrent manic episodes, severe, with psychosis
37178	E111600	Recurrent manic episodes, in full remission
46415	E111z00	Recurrent manic episode NOS
32159	E112400	Single major depressive episode, severe, with psychosis
24171	E113400	Recurrent major depressive episodes, severe, with psychosis
3702	E114.00	Bipolar affective disorder, currently manic
17385	E114.11	Manic-depressive – now manic
35738	E114000	Bipolar affective disorder, currently manic, unspecified
36126	E114100	Bipolar affective disorder, currently manic, mild
46434	E114200	Bipolar affective disorder, currently manic, moderate
63784	E114600	Bipolar affective disorder, currently manic, full remission
4677	E115.00	Bipolar affective disorder, currently depressed
12831	E115.11	Manic-depressive – now depressed
35734	E115100	Bipolar affective disorder, currently depressed, mild
27890	E115200	Bipolar affective disorder, currently depressed, moderate
35607	E115300	Bipolar affect disorder, now depressed, severe, no psychosis
63701	E115400	Bipolar affect disorder, now depressed, severe with psychosis
57465	E115600	Bipolar affective disorder, now depressed, in full remission
37296	E115z00	Bipolar affective disorder, currently depressed, NOS
31316	E116.00	Mixed bipolar affective disorder
31535	E116000	Mixed bipolar affective disorder, unspecified
54195	E116400	Mixed bipolar affective disorder, severe, with psychosis
63651	E116500	Mixed bipolar affective disorder, partial/unspecified remission
55064	E116600	Mixed bipolar affective disorder, in full remission
63583	E116z00	Mixed bipolar affective disorder, NOS
14784	E117.00	Unspecified bipolar affective disorder

TABLE 28 Patient Read codes excluded if there is a diagnosis of severe mental illness or Down syndrome (*continued*)

MedCode	Read code	Read term
49763	E117000	Unspecified bipolar affective disorder, unspecified
68647	E117200	Unspecified bipolar affective disorder, moderate
24230	E117600	Unspecified bipolar affective disorder, in full remission
27986	E117z00	Unspecified bipolar affective disorder, NOS
60178	E11y.00	Other and unspecified manic-depressive psychoses
11596	E11y000	Unspecified manic-depressive psychoses
33426	E11yz00	Other and unspecified manic-depressive psychoses NOS
41992	E11z.00	Other and unspecified affective psychoses
54607	E11z000	Unspecified affective psychoses NOS
33425	E11zz00	Other affective psychosis NOS
4261	E12..00	Paranoid states
14743	E120.00	Simple paranoid state
3890	E121.00	Chronic paranoid psychosis
14971	E122.00	Paraphrenia
50868	E123.11	Folie a deux
31589	E12y.00	Other paranoid states
31455	E12yz00	Other paranoid states NOS
12771	E12z.00	Paranoid psychosis NOS
31984	E13..00	Other nonorganic psychoses
20228	E13..11	Reactive psychoses
8478	E130.00	Reactive depressive psychosis
17770	E130.11	Psychotic reactive depression
29937	E131.00	Acute hysterical psychosis
7332	E132.00	Reactive confusion
15053	E133.00	Acute paranoid reaction
24345	E134.00	Psychogenic paranoid psychosis
16333	E13y.00	Other reactive psychoses
14965	E13z.00	Nonorganic psychosis NOS
3636	E13z.11	Psychotic episode NOS
22188	E1z..00	Non-organic psychosis NOS
61969	E212200	Schizotypal personality
17281	Eu2..00	[X]Schizophrenia, schizotypal and delusional disorders
34236	Eu20.00	[X]Schizophrenia
16764	Eu20000	[X]Paranoid schizophrenia
35877	Eu20213	[X]Schizophrenic catatonia
20785	Eu20400	[X]Post-schizophrenic depression
24107	Eu20511	[X]Chronic undifferentiated schizophrenia
35848	Eu20600	[X]Simple schizophrenia
49420	Eu20y00	[X]Other schizophrenia
94001	Eu20y12	[X]Schizophreniform disord NOS

continued

TABLE 28 Patient Read codes excluded if there is a diagnosis of severe mental illness or Down syndrome (*continued*)

MedCode	Read code	Read term
18053	Eu20y13	[X]Schizophrenifrm psychos NOS
34966	Eu20z00	[X]Schizophrenia, unspecified
39316	Eu21.00	[X]Schizotypal disorder
26859	Eu21.18	[X]Schizotypal personality disorder
28562	Eu22.00	[X]Persistent delusional disorders
34389	Eu22000	[X]Delusional disorder
2113	Eu22011	[X]Paranoid psychosis
11172	Eu22012	[X]Paranoid state
47947	Eu22013	[X]Paraphrenia – late
4843	Eu22015	[X]Paranoia
62405	Eu22100	[X]Delusional misidentification syndrome
55221	Eu22111	[X]Capgras syndrome
101720	Eu22300	[X]Paranoid state in remission
40981	Eu22y11	[X]Delusional dysmorphophobia
50248	Eu22y12	[X]Involutional paranoid state
49223	Eu22z00	[X]Persistent delusional disorder, unspecified
25019	Eu23.00	[X]Acute and transient psychotic disorders
36720	Eu23000	[X]Acute polymorphic psychotic disorder without symptoms of schizophrenia
21455	Eu23012	[X]Cycloid psychosis
26143	Eu23112	[X]Cycloid psychosis with symptoms of schizophrenia
44307	Eu23300	[X]Other acute predominantly delusional psychotic disorders
27770	Eu23312	[X]Psychogenic paranoid psychosis
44503	Eu23y00	[X]Other acute and transient psychotic disorders
34168	Eu23z00	[X]Acute and transient psychotic disorder, unspecified
31707	Eu23z11	[X]Brief reactive psychosis NOS
29651	Eu23z12	[X]Reactive psychosis
105606	Eu24.11	[X]Folie a deux
11973	Eu24.13	[X]Induced psychotic disorder
9422	Eu25.00	[X]Schizoaffective disorders
33847	Eu25000	[X]Schizoaffective disorder, manic type
16905	Eu25011	[X]Schizoaffective psychosis, manic type
51903	Eu25012	[X]Schizophreniform psychosis, manic type
11055	Eu25100	[X]Schizoaffective disorder, depressive type
35274	Eu25111	[X]Schizoaffective psychosis, depressive type
33693	Eu25200	[X]Schizoaffective disorder, mixed type
37580	Eu25212	[X]Mixed schizophrenic and affective psychosis
58532	Eu25y00	[X]Other schizoaffective disorders
37681	Eu25z00	[X]Schizoaffective disorder, unspecified
33410	Eu25z11	[X]Schizoaffective psychosis NOS
101987	Eu26.00	[X]Nonorganic psychosis in remission

TABLE 28 Patient Read codes excluded if there is a diagnosis of severe mental illness or Down syndrome (*continued*)

MedCode	Read code	Read term
30985	Eu2y.00	[X]Other nonorganic psychotic disorders
31738	Eu2y.11	[X]Chronic hallucinatory psychosis
11244	Eu2z.00	[X]Unspecified nonorganic psychosis
694	Eu2z.11	[X]Psychosis NOS
5726	Eu3..00	[X]Mood – affective disorders
12173	Eu30.00	[X]Manic episode
9521	Eu30.11	[X]Bipolar disorder, single manic episode
2741	Eu30000	[X]Hypomania
13024	Eu30100	[X]Mania without psychotic symptoms
21065	Eu30200	[X]Mania with psychotic symptoms
48632	Eu30212	[X]Mania with mood-incongruent psychotic symptoms
32088	Eu30y00	[X]Other manic episodes
44513	Eu30z00	[X]Manic episode, unspecified
4678	Eu30z11	[X]Mania NOS
6874	Eu31.00	[X]Bipolar affective disorder
1531	Eu31.11	[X]Manic-depressive illness
6710	Eu31.12	[X]Manic-depressive psychosis
16808	Eu31000	[X]Bipolar affective disorder, current episode hypomanic
26299	Eu31100	[X]Bipolar affect disorder current episode manic wout psychotic symptoms
28277	Eu31200	[X]Bipolar affect disorder current episode manic with psychotic symptoms
16562	Eu31300	[X]Bipolar affect disorder current episode mild or moderate depress
23713	Eu31400	[X]Bipol affect disorder current episode severe depress, no psychotic symptoms
4732	Eu31500	[X]Bipolar affect disorder current episode severe depress with psychotic symptoms
27584	Eu31700	[X]Bipolar affective disorder, currently in remission
103915	Eu31900	[X]Bipolar affective disorder type II
53840	Eu31y00	[X]Other bipolar affective disorders
73924	Eu31y11	[X]Bipolar II disorder
51032	Eu31y12	[X]Recurrent manic episodes
33751	Eu31z00	[X]Bipolar affective disorder, unspecified
12099	Eu32300	[X]Severe depressive episode with psychotic symptoms
24117	Eu32311	[X]Single episode of major depression and psychotic symptoms
52678	Eu32312	[X]Single episode of psychogenic depressive psychosis
24112	Eu32313	[X]Single episode of psychotic depression
28863	Eu32314	[X]Single episode of reactive depressive psychosis
98417	Eu32800	[X]Major depression, severe with psychotic symptoms
29451	Eu33213	[X]Manic-depress psychosis, depress, no psychotic symptoms
47009	Eu33300	[X]Recurrent depress disorder current episode severe with psychotic symptoms
23731	Eu33311	[X]Endogenous depression with psychotic symptoms
28677	Eu33312	[X]Manic-depress psychosis, depressed type + psychotic symptoms
32941	Eu33313	[X]Recurrent severe episodes/major depression + psychotic symptom

continued

TABLE 28 Patient Read codes excluded if there is a diagnosis of severe mental illness or Down syndrome (*continued*)

MedCode	Read code	Read term
31757	Eu33314	[X]Recurrent severe episodes/psychogenic depressive psychosis
16861	Eu33315	[X]Recurrent severe episodes of psychotic depression
37764	Eu33316	[X]Recurrent severe episodes/reactive depressive psychosis
31633	Eu3z.11	[X]Affective psychosis NOS
28168	Eu44.14	[X]Hysterical psychosis

NOS, not otherwise stated.

Exclusions: sleep apnoea, sleep-related respiratory failure, or alcohol abuse

Patients will be excluded if they are diagnosed with sleep apnoea, sleep-related respiratory failure, or alcohol abuse on or before their index date (*Table 29*).

TABLE 29 Patients Read codes excluded if there is a diagnosis of sleep apnoea, sleep-related respiratory failure, or alcohol abuse on or before their index date

MedCode	Read code	Read term
8430	1462	H/O: alcoholism
16237	E01..00	Alcoholic psychoses
16225	E010.00	Alcohol withdrawal delirium
22277	E010.11	DTs – delirium tremens
1476	E010.12	Delirium tremens
20762	E011.00	Alcohol amnestic syndrome
4500	E011000	Korsakov's alcoholic psychosis
11106	E011100	Korsakov's alcoholic psychosis with peripheral neuritis
18636	E011200	Wernicke-Korsakov syndrome
41920	E011z00	Alcohol amnestic syndrome NOS
54505	E012.00	Other alcoholic dementia
27342	E012.11	Alcoholic dementia NOS
37946	E012000	Chronic alcoholic brain syndrome
25110	E013.00	Alcohol withdrawal hallucinosis
57939	E014.00	Pathological alcohol intoxication
20407	E014.11	Drunkenness – pathological
30404	E015.00	Alcoholic paranoia
33670	E01y.00	Other alcoholic psychosis
2082	E01y000	Alcohol withdrawal syndrome
68111	E01yz00	Other alcoholic psychosis NOS
67651	E01z.00	Alcoholic psychosis NOS
2084	E23..00	Alcohol dependence syndrome
2081	E23..11	Alcoholism
1399	E23..12	Alcohol problem drinking

TABLE 29 Patients Read codes excluded if there is a diagnosis of sleep apnoea, sleep-related respiratory failure, or alcohol abuse on or before their index date (*continued*)

MedCode	Read code	Read term
5740	E230.00	Acute alcoholic intoxication in alcoholism
57714	E230.11	Alcohol dependence with acute alcoholic intoxication
40530	E230000	Acute alcoholic intoxication, unspecified, in alcoholism
56947	E230100	Continuous acute alcoholic intoxication in alcoholism
21624	E230200	Episodic acute alcoholic intoxication in alcoholism
59574	E230300	Acute alcoholic intoxication in remission, in alcoholism
36296	E230z00	Acute alcoholic intoxication in alcoholism NOS
31443	E231.00	Chronic alcoholism
37605	E231.11	Dipsomania
43193	E231000	Unspecified chronic alcoholism
24064	E231100	Continuous chronic alcoholism
26106	E231200	Episodic chronic alcoholism
24485	E231300	Chronic alcoholism in remission
33635	E231z00	Chronic alcoholism NOS
6169	E23z.00	Alcohol dependence syndrome NOS
39327	Eu10200	[X]Mental and behaviour disorder due to use alcohol: dependence syndrome
28780	Eu10211	[X]Alcohol addiction
5758	Eu10212	[X]Chronic alcoholism
69691	Eu10213	[X]Dipsomania
20514	Eu10300	[X]Mental and behaviour disorder due to use alcohol: withdrawal state
64101	Eu10400	[X]Men and behaviour disorder due alcohol: withdrawal state with delirium
17259	Eu10411	[X]Delirium tremens, alcohol induced
6467	Eu10511	[X]Alcoholic hallucinosis
65932	Eu10512	[X]Alcoholic jealousy
30162	Eu10513	[X]Alcoholic paranoia
17607	Eu10514	[X]Alcoholic psychosis NOS
11670	Eu10611	[X]Korsakov's psychosis, alcohol induced
26323	Eu10711	[X]Alcoholic dementia NOS
37691	Eu10712	[X]Chronic alcoholic brain syndrome
47555	F11x000	Cerebral degeneration due to alcoholism
36748	F11x011	Alcoholic encephalopathy
33839	F144000	Cerebellar ataxia due to alcoholism
2925	F375.00	Alcoholic polyneuropathy
31742	F394100	Alcoholic myopathy
7603	Fy03.00	Sleep apnoea
8148	Fy03.11	Obstructive sleep apnoea
38686	Fy04.00	Sleep-related respiratory failure
59155	Fy04.11	Ondine's curse
4915	G555.00	Alcoholic cardiomyopathy

continued

TABLE 29 Patients Read codes excluded if there is a diagnosis of sleep apnoea, sleep-related respiratory failure, or alcohol abuse on or before their index date (*continued*)

MedCode	Read code	Read term
8363	G852300	Oesophageal varices in alcoholic cirrhosis of the liver
23779	H5B..00	Sleep apnoea
20748	H5B0.00	Obstructive sleep apnoea
4506	J153.00	Alcoholic gastritis
10691	J610.00	Alcoholic fatty liver
3216	J611.00	Acute alcoholic hepatitis
4743	J612.00	Alcoholic cirrhosis of liver
21713	J612000	Alcoholic fibrosis and sclerosis of liver
7885	J613.00	Alcoholic liver damage unspecified
17330	J613000	Alcoholic hepatic failure
7943	J617.00	Alcoholic hepatitis
7602	J617000	Chronic alcoholic hepatitis
24984	J671000	Alcohol-induced chronic pancreatitis
48539	R005100	[D]Insomnia with sleep apnoea
36301	R005300	[D]Hypersomnia with sleep apnoea
2506	R005311	[D]Sleep apnoea syndrome
20438	R005312	[D]Syndrome sleep apnoea
7123	ZV11300	[V]Personal history of

NOS, not otherwise stated.

Exclusions: neuropathic pain

Patients will be excluded if they are diagnosed with neuropathic pain in the 12 months on or before their index date (*Table 30*).

TABLE 30 Patient Read code excluded if there is a diagnosis of neuropathic pain in the last 12 months on or before the index date

MedCode	Read code	Read term
1598	A531.11	Post herpetic neuralgia
27403	A531100	Geniculate herpes zoster
7331	A531111	Ramsay – Hunt syndrome
11498	A531200	Postherpetic trigeminal neuralgia
31709	A531300	Postherpetic polyneuropathy
17180	A531500	Postzoster neuralgia
10223	A531511	Postherpetic neuralgia
28333	C373200	Familial neuropathic amyloid
7584	F300.00	Post-herpetic trigeminal neuralgia
1541	F301.00	Other specified trigeminal neuralgia
4912	F301000	Tic douloureux

TABLE 30 Patient Read code excluded if there is a diagnosis of neuropathic pain in the last 12 months on or before the index date (*continued*)

MedCode	Read code	Read term
6581	F301z00	Trigeminal neuralgia NOS
18016	F336000	Phantom limb syndrome with pain
23768	F337.00	Nerve root and plexus compressions in diseases EC
55335	F337000	Nerve root and plexus compressions in neoplastic disease
33604	F337100	Nerve root and plexus compressions in intervertion discussion disorder
23699	F337200	Nerve root and plexus compressions in spondylosis
24410	F337300	Nerve root and plexus compressions in other dorsopathies
56272	F374.00	Polyneuropathy in disease EC
39692	F374400	Polyneuropathy in herpes zoster
63555	F374z00	Polyneuropathy in disease NOS
93868	Fyu6A00	[X]Other mononeuropathies of upper limb
72922	Fyu6B00	[X]Other mononeuropathies of lower limb
91741	Fyu6C00	[X]Other specified mononeuropathies
107322	Fyu6D00	[X]Other mononeuropathies in diseases classified elsewhere
22238	Fyu6E00	[X]Ilio-inguinal nerve entrapment
55076	Fyu7.00	[X]Polyneuropathies & other disorder of peripheral nervous system
97449	Fyu7000	[X]Other hereditary and idiopathic neuropathies
97479	Fyu7100	[X]Other inflammatory polyneuropathies
97306	Fyu7200	[X]Other specified polyneuropathies
39858	Fyu7B00	[X]Inflammatory polyneuropathy, unspecified
35537	Fyu7C00	[X] Polyneuropathy, unspecified
99855	M271700	Neuropathic foot ulcer
49575	N035.00	Neuropathic arthropathy
8710	N035.11	Charcot's arthropathy
36643	N035.12	Neuropathic arthritis
37759	N11y200	Neuropathic spondylopathy l
54992	N242.00	Neuralgia, neuritis and radiculitis unspecified
2284	N242000	Neuralgia unspecified
1416	N242100	Neuritis unspecified
769	N242200	Radiculitis unspecified
11544	N242300	Neuropathic pain
23839	N242z00	Neuralgia, neuritis or radiculitis NOS
41736	N242z11	Policeman's disease
18492	SD72200	Neuropathic foot blister

EC, elsewhere classified; NOS, not otherwise stated.

Outcomes: codes for the hospital admission and death certificate data

The following ICD-10 codes were used to identify the following outcomes in the HES or ONS data:

- fracture: S02, S12, S22, S32, S42, S52, S62, S72, S82 or S92
- hip fracture: S72.0, S27.1 or S72.2
- forearm/wrist/hand fracture: S52 or S62
- fall: W0 or W1
- acute bacterial infection: A4, B95, B96, H05.0, H60.1, K12.2, L03, J15, J18, N30.0, N30.2, N30.8, N30.9 or N39.0
- UTI or acute LRTI: J15, J18, N30.0, N30.2, N30.8, N30.9 or N39.0
- ischaemic stroke/TIA: G45 or I63
- venous thromboembolism: I26, I80, I81 or I82
- agitation/psychosis: R44, F29, R45.1, R45.4, R45.5, R45.6 or F06.0.

Outcomes: Read codes in the Clinical Practice Research Datalink

Tables 31–38 show the Read codes that were used to identify outcomes in the CPRD.

TABLE 31 Read codes used to identify hip fractures

MedCode	Read code	Read term
9792	7K1D01E	DHS – Dynamic hip screw primary fixation of neck of femur
12544	7K1D01F	Dynamic hip screw primary fixation of neck of femur
6660	7K1L400	Closed reduction of fracture of hip
2225	S30..00	Fracture of neck of femur
1994	S30..11	Hip fracture
19387	S302011	Closed fracture of femur, greater trochanter
8648	S302400	Closed fracture of femur, intertrochanteric
8243	S305.00	Subtrochanteric fracture
24276	S30w.00	Closed fracture of unspecified proximal femur
18273	S30y.00	Closed fracture of neck of femur NOS
10570	S30y.11	Hip fracture NOS

NOS, not otherwise stated.

TABLE 32 Read codes used to identify forearm, wrist and hand fracture

MedCode	Read code	Read term
8885	7K1LJ00	Closed reduction of fracture of thumb
6942	7K1LL00	Closed reduction of fracture of radius and or ulna
5951	7K1LM00	Closed reduction of fracture of wrist
1250	S224.11	Elbow fracture – closed
6825	S23..00	Fracture of radius and ulna
43570	S230.00	Closed fracture of proximal radius and ulna
7009	S230600	Closed fracture radius, head
18299	S234.00	Closed fracture of radius and ulna, lower end
203	S234.11	Wrist fracture – closed
343	S234100	Closed Colles' fracture
1742	S234200	Closed fracture of the distal radius, unspecified
9165	S234300	Closed fracture of ulna, styloid process
40476	S234500	Closed fracture distal ulna, unspecified
199	S23B.00	Fracture of lower end of radius
137	S23x111	Fracture of radius NOS
1073	S23x211	Fracture of ulna NOS
909	S23z.00	Fracture of radius and ulna, NOS
22375	S24..00	Fracture of carpal bone
15666	S240.00	Closed fracture of carpal bone
8056	S242.00	Fracture at wrist and hand level
553	S242000	Fracture of scaphoid
993	S242200	Fracture of other metacarpal bone
25519	S250300	Closed fracture finger metacarpal shaft
12546	S250400	Closed fracture finger metacarpal neck
29111	S251.00	Open fracture of metacarpal bone(s)
441	S26..00	Fracture of one or more phalanges of hand
5260	S26..11	Finger fracture
8302	S260.00	Closed fracture of one or more phalanges of hand
24516	S260D00	Closed fracture finger proximal phalanx
7500	S262.00	Fracture of thumb
6299	S263.00	Fracture of other finger
4582	S26z.00	Fracture of one or more phalanges of hand NOS
18614	S4C..00	Fracture-dislocation or subluxation of wrist
10250	S4D..00	Fracture-dislocation/subluxation finger/thumb

NOS, not otherwise stated.

TABLE 33 Read codes used to identify fractures (and any of the above codes for hip, forearm, wrist and hand fracture)

MedCode	Read code	Read term
18962	7K1L500	Closed reduction of fracture of femur
6106	7K1L800	Closed reduction of fracture of ankle
7339	7K1LA00	Closed reduction of fracture of toe
6379	7K1LF00	Closed reduction of fracture of humerus
7428	7K1LG00	Closed reduction of fracture of shoulder
5526	N331.00	Pathological fracture
30616	N331000	Pathological fracture of thoracic vertebra
17377	N331800	Osteoporosis + pathological fracture lumbar vertebrae
12673	N331900	Osteoporosis + pathological fracture thoracic vertebrae
11543	N331G00	Collapse of lumbar vertebra
45736	N331H00	Collapse of cervical vertebra due to osteoporosis
4013	N331L00	Collapse of vertebra due to osteoporosis NOS
11503	N331M00	Fragility fracture due to unspecified osteoporosis
93497	N331N00	Fragility fracture
4409	S10..12	Fracture of vertebra without spinal cord lesion
11296	S100.00	Closed fracture of cervical spine
39887	S100A00	Closed fracture axis, odontoid process
3888	S104.00	Closed fracture lumbar vertebra
8266	S104100	Closed fracture lumbar vertebra, wedge
34403	S10A100	Fracture of second cervical vertebra
9072	S10B400	Fracture of acetabulum
280	S120.00	Closed fracture rib
7831	S120000	Closed fracture of rib, unspecified
9688	S127.00	Fracture of rib
738	S13..00	Fracture or disruption of pelvis
5302	S132.00	Closed fracture pubis
7004	S132000	Closed fracture pelvis, single pubic ramus
6667	S132100	Closed fracture pelvis, multiple pubic rami – stable
46592	S132200	Closed fracture pelvis, multiple pubic rami – unstable
28702	S132z00	Closed fracture pubis NOS
28375	S13y.00	Closed fracture of pelvis NOS
11277	S150.00	Multiple fractures of thoracic spine
6195	S2...00	Fracture of upper limb
5929	S2...11	Arm fracture
483	S20..00	Fracture of clavicle
44715	S200000	Closed fracture of clavicle, unspecified part
29899	S200300	Closed fracture clavicle, lateral end
1177	S21..00	Fracture of scapula
10735	S21..11	Shoulder blade fracture
517	S22..00	Fracture of humerus
11222	S220.00	Closed fracture of the proximal humerus
44721	S220000	Closed fracture of proximal humerus, unspecified part

TABLE 33 Read codes used to identify fractures (and any of the above codes for hip, forearm, wrist and hand fracture) (*continued*)

MedCode	Read code	Read term
11313	S220100	Closed fracture proximal humerus, neck
11044	S220300	Closed fracture proximal humerus, greater tuberosity
6893	S224100	Closed fracture distal humerus, supracondylar
1548	S228.00	Fracture of lower end of humerus
10382	S22z.00	Fracture of humerus NOS
8891	S3...00	Fracture of lower limb
8040	S31..00	Other fracture of femur
6868	S310.00	Closed fracture of femur, shaft or unspecified part
37662	S310000	Closed fracture of femur, unspecified part
12791	S310011	Thigh fracture NOS
6320	S312100	Closed fracture of femoral condyle, unspecified
5332	S312300	Closed fracture distal femur, supracondylar
8646	S314.00	Fracture of shaft of femur
8589	S315.00	Fracture of lower end of femur
520	S31z.00	Fracture of femur, NOS
235	S32..00	Fracture of patella
27719	S334.00	Closed fracture distal tibia
6839	S339000	Closed fracture of distal fibula
78444	S33A.00	Fracture of tibia
4304	S33x100	Closed fracture of fibula, unspecified part, NOS
4572	S33x200	Closed fracture of tibia and fibula, unspecified part
325	S34..00	Fracture of ankle
7135	S342000	Closed fracture ankle, lateral malleolus, low
7317	S344.00	Closed fracture ankle, bimalleolar
169	S35..11	Metatarsal bone fracture
2710	S35..12	Tarsal bone fracture
8276	S350.00	Closed fracture of calcaneus
3937	S352700	Closed fracture metatarsal
35077	S352E00	Closed fracture metatarsal head
6062	S356.00	Fracture of metatarsal bone
2176	S362.00	Fracture of great toe
2470	S3z..00	Fracture of unspecified bones
358	S3z..11	Fracture NOS
34212	S4J2100	Closed fracture-subluxation of pelvis

NOS, not otherwise stated.

TABLE 34 Read codes used to identify falls

MedCode	Read code	Read term
6008	16D..00	Falls
8694	16D1.00	Recurrent falls
46559	16D2.00	Number of falls in last year
98223	16D5.00	Fall onto outstretched hand
108062	16D6.00	Fall
5284	1B65.00	Had a collapse
1634	1B65.11	Collapse – symptom
10412	224..00	O/E – collapsed
105499	8CMW400	Falls care pathway
2307	R002.00	[D]Syncope and collapse
1812	R002300	[D]Collapse
4859	R200.12	[D] Geriatric fall
6815	TC...00	Accidental falls
384	TC...11	Fall – accidental
38818	TC42000	Fall from chair
26432	TC42100	Fall from bed
15112	TC5..00	Fall on same level from slipping, tripping or stumbling
18007	TC50.00	Fall on same level from slipping
7948	TC52.00	Fall on same level from stumbling
8730	TCy..00	Other falls
11308	TCyz.00	Other accidental fall NOS
6835	TCz..00	Accidental falls NOS
7970	U10..00	[X]Falls
43191	U10J000	[X]Other fall on same level, occurrence at home
24776	U10z.00	[X]Unspecified fall

NOS, not otherwise stated; O/E, on examination.

TABLE 35 Read codes used to identify UTIs or LRTIs

MedCode	Read code	Read term
23640	H0y..00	Other specified acute respiratory infections
21113	H0z..00	Acute respiratory infection NOS
10086	H2...00	Pneumonia and influenza
1849	H21..00	Lobar (pneumococcal) pneumonia
12061	H22y200	Pneumonia – *Legionella*
23095	H22z.00	Bacterial pneumonia NOS
25694	H23..00	Pneumonia due to other specified organisms
886	H25..00	Bronchopneumonia due to unspecified organism
16287	H25..11	Chest infection – unspecified bronchopneumonia
572	H26..00	Pneumonia due to unspecified organism
9639	H260.00	Lobar pneumonia due to unspecified organism
3683	H261.00	Basal pneumonia due to unspecified organism
5324	H28..00	Atypical pneumonia
104121	H2B..00	Community acquired pneumonia
389	K15..00	Cystitis
15074	K150.00	Acute cystitis
1353	K155.00	Recurrent cystitis
22682	K15y000	Cystitis cystica
34645	K15y200	Abscess of bladder
1289	K190.00	Urinary tract infection, site not specified
1572	K190.11	Recurrent urinary tract infection
4453	K190100	Pyuria, site not specified
10515	K190300	Recurrent urinary tract infection
2985	K190311	Recurrent UTI
97002	K190500	Urinary tract infection
104141	K190600	Urosepsis
150	K190z00	Urinary tract infection, site not specified NOS
2465	K193.00	Urethral caruncle
507	K197.00	Haematuria
19361	K197.11	Traumatic haematuria
2784	K197200	Microscopic haematuria
7232	K197300	Frank haematuria
5264	K19y300	Pneumaturia
7733	K19y411	Urethral bleeding

NOS, not otherwise stated.

TABLE 36 Read codes used to identify infection, including any of the codes for UTIs or LRTIs (see *Table 35*)

MedCode	Read code	Read term
885	A38..00	Septicaemia
30102	A381000	Septicaemia due to *Staphylococcus aureus*
10872	A384200	*Escherichia coli* septicaemia
23991	A384211	*E. coli* septicaemia
33765	A38z.00	Septicaemia NOS
2136	A38z.11	Sepsis
3382	A3B0.00	Streptococcal infection
1426	A3B1.00	Staphylococcal infection
8673	A3B1100	Meticillin resistant staphylococcus aureus
5534	A3B2.00	Pneumococcal infection
12062	A3B4.00	*E. coli* infection
8329	A3B4.11	*E. coli* infection
6856	A3B7.00	*Pseudomonas* infection
105405	A3BC.00	Infection due to ESBL producing bacteria
5945	A3By800	Coliform bacteria
104028	A3C..00	Sepsis
104150	A3Cy.00	Other specified sepsis
4328	F4G0100	Orbital cellulitis
8852	F501112	Cellulitis, external ear
4456	K284300	Cellulitis of scrotum
4779	M020.00	Cellulitis and abscess of finger
3527	M020000	Cellulitis and abscess of finger unspecified
3960	M021.00	Cellulitis and abscess of toe
3363	M021000	Cellulitis and abscess of toe unspecified
16536	M03..00	Other cellulitis and abscess
3998	M030.00	Cellulitis and abscess of face
10485	M030111	Cellulitis and abscess of nose
1874	M032200	Cellulitis and abscess of back
14937	M032400	Cellulitis and abscess of umbilicus
3461	M033.00	Cellulitis and abscess of arm
1415	M034.11	Cellulitis and abscess of hand
2914	M034000	Cellulitis and abscess of hand unspecified
7865	M036.00	Cellulitis and abscess of leg excluding foot
10326	M036.11	Cellulitis and abscess of leg
25890	M036300	Cellulitis and abscess of lower leg
680	M036z00	Cellulitis and abscess of leg NOS
2089	M037000	Cellulitis and abscess of foot unspecified
7328	M037200	Cellulitis in diabetic foot
309	M03z.00	Cellulitis and abscess NOS
4207	M03z000	Cellulitis NOS
943	M05..00	Impetigo
14934	M05z.00	Impetigo NOS

TABLE 36 Read codes used to identify infection, including any of the codes for UTIs or LRTIs (see *Table 35*) (*continued*)

MedCode	Read code	Read term
6833	M08..00	Cutaneous cellulitis
1315	M081.00	[X]Cellulitis of other parts of limb
6368	M085.00	Cellulitis of leg
7684	M08B.00	Cellulitis of foot
94868	M08C.00	Cellulitis of toe

ESBL, extended-spectrum beta-lactamase; NOS, not otherwise stated.

TABLE 37 Read codes used to identify ischaemic stroke and TIA

MedCode	Read code	Read term
8837	G64..00	Cerebral arterial occlusion
5363	G64..11	CVA – cerebral artery occlusion
569	G64..12	Infarction – cerebral
6155	G64..13	Stroke due to cerebral arterial occlusion
16517	G640.00	Cerebral thrombosis
36717	G640000	Cerebral infarction due to thrombosis of cerebral arteries
3149	G64z.00	Cerebral infarction NOS
5602	G64z.12	Cerebellar infarction
10504	G64z300	Right-sided cerebral infarction
504	G65..00	Transient cerebral ischaemia
3132	G65..11	Drop attack
1433	G65..12	Transient ischaemic attack
1469	G66..00	Stroke and cerebrovascular accident unspecified
1298	G66..11	CVA unspecified
6253	G66..12	Stroke unspecified
6116	G66..13	CVA – cerebrovascular accident unspecified
51767	G666.00	Pure sensory lacunar syndrome
12833	G668.00	Right-sided CVA

CVA, cerebrovascular accident; NOS, not otherwise stated.

TABLE 38 Read codes used to identify venous thromboembolism

MedCode	Read code	Read term
94552	8HTm.00	Referral to deep-vein thrombosis clinic
1266	G401.00	Pulmonary embolism
9701	G401.12	Pulmonary embolus
3576	G801.00	Deep-vein phlebitis and thrombophlebitis of the leg
824	G801.11	Deep-vein thrombosis
3392	G801.13	DVT – deep-vein thrombosis
15382	G801600	Thrombophlebitis of the femoral vein
22038	G801D00	Deep-vein thrombosis of lower limb
100103	G824.00	Axillary vein thrombosis

DVT, deep-vein thrombosis.

Appendix 2 Additional primary care patient characteristics

TABLE 39 Further patient characteristics, comorbidities and concurrent medications, by first sleep disturbance prescription

Characteristic	First sleep disturbance treatment			
	Z-drug (*N* = 2952)	Low-dose TCA (*N* = 1898)	BZD (*N* = 308)	No drug (*N* = 1651)
Dementia				
Months since dementia diagnosis, median (IQR)[a]	11.6 (3.5–26.2)	12.5 (4.2–27.2)	11.6 (3.6–26.2)	11.4 (4.1–24.6)
Dementia subtype, *n* (%)				
Alzheimer's disease	1135 (38)	790 (42)	116 (38)	643 (39)
Vascular dementia	800 (27)	529 (28)	72 (23)	452 (27)
Other/mixed dementia	309 (10)	159 (8)	34 (11)	172 (10)
Unspecified dementia/missing	708 (24)	420 (22)	86 (28)	384 (23)
Anticholinesterase/memantine prescription in last 90 days, *n* (%)	670 (23)	485 (26)	51 (17)	313 (19)
Antipsychotic prescription in last 90 days, *n* (%)	542 (18)	229 (12)	46 (15)	282 (17)
Agitation/psychosis history, *n* (%)	484 (16)	292 (15)	75 (24)	369 (22)
End-of-life care, *n* (%)	160 (5)	110 (6)	11 (4)	73 (4)
Sleep disturbance, *n* (%)				
Sleep disturbance diagnosis pre dementia	644 (22)	335 (18)	65 (21)	532 (32)
History of BZD use	718 (24)	468 (25)	89 (29)	299 (18)
History of Z-drug use	258 (9)	107 (6)	18 (6)	90 (5)
Medical history in past year				
Falls, *n* (%)	820 (28)	440 (23)	82 (27)	473 (29)
Fractures, *n* (%)	309 (10)	153 (8)	27 (9)	117 (7)
Dizziness/unsteadiness, *n* (%)	157 (5)	101 (5)	17 (6)	108 (7)
Faints/syncope, *n* (%)	152 (5)	86 (5)	26 (8)	103 (6)
UTI/acute LRTI, *n* (%)	766 (26)	441 (23)	77 (25)	368 (22)
Influenza vaccination, *n* (%)	2049 (69)	1438 (76)	220 (71)	1185 (72)
Pneumonia vaccination, *n* (%)	138 (5)	75 (4)	13 (4)	97 (6)
Physician consultations, mean (SD)	8.4 (7.3)	8.9 (7.1)	7.8 (6.7)	7.6 (6.7)
Hospital admissions, mean (SD)	1.2 (1.9)	1.1 (1.7)	1.2 (1.8)	0.9 (2.1)
Comorbidities, *n* (%)				
Depression	705 (24)	500 (26)	76 (25)	422 (26)
Depression symptoms	533 (18)	425 (22)	52 (17)	311 (19)
Anxiety	458 (16)	322 (17)	58 (19)	269 (16)
Anxiety symptoms	353 (12)	291 (15)	37 (12)	214 (13)

continued

TABLE 39 Further patient characteristics, comorbidities and concurrent medications, by first sleep disturbance prescription (*continued*)

Characteristic	First sleep disturbance treatment			
	Z-drug (*N* = 2952)	Low-dose TCA (*N* = 1898)	BZD (*N* = 308)	No drug (*N* = 1651)
Parkinson's disease	170 (6)	72 (4)	21 (7)	103 (6)
Urinary incontinence	424 (14)	342 (18)	59 (19)	425 (26)
Benign prostatic hyperplasia	310 (11)	177 (9)	36 (12)	156 (9)
Asthma	292 (10)	212 (11)	26 (8)	143 (9)
Cancer	627 (21)	399 (21)	64 (21)	290 (18)
COPD	223 (8)	181 (10)	23 (7)	120 (7)
Osteoporosis	332 (11)	265 (14)	39 (13)	186 (11)
Other musculoskeletal conditions	363 (12)	265 (14)	51 (17)	211 (13)
Osteoarthritis/rheumatoid arthritis	1160 (39)	855 (45)	116 (38)	664 (40)
Other joint conditions	2426 (82)	1604 (85)	245 (80)	1383 (84)
Headache/migraine	578 (20)	489 (26)	44 (14)	318 (19)
Back/neck pain	1588 (54)	1198 (63)	150 (49)	876 (53)
ARMD	167 (6)	130 (7)	25 (8)	100 (6)
Cataract	832 (28)	585 (31)	84 (27)	479 (29)
Glaucoma	288 (10)	205 (11)	26 (8)	158 (10)
Retinal disorder	248 (8)	176 (9)	28 (9)	122 (7)
Diabetes	432 (15)	302 (16)	44 (14)	218 (13)
Hyperlipidaemia	380 (13)	296 (16)	40 (13)	247 (15)
Hypertension	1521 (52)	1082 (57)	151 (49)	902 (55)
Stroke/TIA	644 (22)	404 (21)	65 (21)	353 (21)
Myocardial infarction	247 (8)	159 (8)	29 (9)	157 (10)
Heart failure	254 (9)	138 (7)	27 (9)	168 (10)
Atrial fibrillation	454 (15)	273 (14)	46 (15)	235 (14)
Angina	435 (15)	279 (15)	44 (14)	278 (17)
Venous thromboembolism	189 (6)	139 (7)	24 (8)	103 (6)
Prescriptions in last 90 days				
SSRI	610 (21)	341 (18)	50 (16)	298 (18)
Other antidepressant	183 (6)	93 (5)	15 (5)	122 (7)
Antiepileptic	174 (6)	135 (7)	40 (13)	91 (6)
Analgesic	1249 (42)	1049 (55)	114 (37)	590 (36)
Inhaled corticosteroid	124 (4)	108 (6)	14 (5)	71 (4)
Lipid-regulating medication	986 (33)	712 (38)	88 (29)	532 (32)
Diuretic	917 (31)	583 (31)	90 (29)	520 (31)
Beta-blocker	527 (18)	327 (17)	51 (17)	270 (16)
ACE inhibitor	574 (19)	437 (23)	62 (20)	322 (20)
Angiotensin II receptor antagonist	193 (7)	157 (8)	19 (6)	109 (7)
Calcium channel blocker	526 (18)	389 (20)	38 (12)	295 (18)
Anticoagulant	149 (5)	121 (6)	12 (4)	84 (5)
Antiplatelet	1296 (44)	814 (43)	121 (39)	753 (46)

TABLE 39 Further patient characteristics, comorbidities and concurrent medications, by first sleep disturbance prescription (*continued*)

Characteristic	First sleep disturbance treatment			
	Z-drug (*N* = 2952)	Low-dose TCA (*N* = 1898)	BZD (*N* = 308)	No drug (*N* = 1651)
Cardiac glycoside	234 (8)	122 (6)	26 (8)	124 (8)
NSAID	209 (7)	223 (12)	32 (10)	96 (6)
Bisphosphonate	278 (9)	248 (13)	24 (8)	143 (9)
Calcium/vitamin D	514 (17)	398 (21)	44 (14)	282 (17)
Antibiotic (in last 30 days)	622 (21)	376 (20)	56 (18)	287 (17)

ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease.

TABLE 40 Adjusted ORs for the association between patient characteristics and sleep disturbance treatment

Characteristic	Z-drug		Low-dose TCA		BZD	
	OR[a] (95% CI)	*p*-value	OR[a] (95% CI)	*p*-value	OR[a] (95% CI)	*p*-value
Women	0.85 (0.73 to 0.98)	0.02	1.00 (0.85 to 1.17)	0.99	0.75 (0.58 to 0.96)	0.02
Age (years), per year	1.00 (0.99 to 1.01)	0.41	0.99 (0.98 to 1.00)	0.07	1.01 (0.99 to 1.02)	0.56
Care home resident						
No	1.00		1.00		1.00	
Yes	1.07 (0.90 to 1.27)	0.45	1.02 (0.84 to 1.24)	0.83	0.83 (0.61 to 1.12)	0.23
Missing	1.33 (1.15 to 1.55)	< 0.01	1.40 (1.18 to 1.65)	< 0.01	1.23 (0.94 to 1.60)	0.13
Index date (per year)	1.05 (1.03 to 1.07)	< 0.01	1.07 (1.05 to 1.09)	< 0.01	0.96 (0.93 to 0.99)	0.02
Region						
North East	1.00		1.00		1.00	
North West	2.30 (1.49 to 3.54)	< 0.01	1.46 (0.96 to 2.24)	0.08	0.65 (0.34 to 1.24)	0.19
Yorkshire and The Humber	2.58 (1.52 to 4.40)	< 0.01	1.26 (0.73 to 2.18)	0.41	1.28 (0.58 to 2.80)	0.54
East Midlands	1.25 (0.73 to 2.12)	0.41	0.61 (0.34 to 1.07)	0.09	0.73 (0.33 to 1.58)	0.42
West Midlands	1.99 (1.28 to 3.10)	< 0.01	0.71 (0.45 to 1.11)	0.13	0.49 (0.24 to 0.97)	0.04
East of England	1.60 (1.02 to 2.52)	0.04	0.69 (0.44 to 1.09)	0.11	0.71 (0.36 to 1.40)	0.33
South West	2.42 (1.55 to 3.78)	< 0.01	1.33 (0.86 to 2.08)	0.20	1.02 (0.53 to 1.97)	0.94
South Central	2.05 (1.30 to 3.24)	< 0.01	1.72 (1.09 to 2.71)	0.02	0.94 (0.48 to 1.87)	0.87
London	2.36 (1.48 to 3.78)	< 0.01	0.81 (0.50 to 1.31)	0.39	0.48 (0.23 to 1.02)	0.06
South East Coast	3.37 (2.10 to 5.41)	< 0.01	0.93 (0.57 to 1.52)	0.78	1.00 (0.49 to 2.04)	1.00
IMD quintile						
1	1.00		1.00		1.00	
2	0.91 (0.71 to 1.15)	0.42	1.00 (0.77 to 1.29)	0.99	0.75 (0.50 to 1.12)	0.16
3	0.95 (0.75 to 1.20)	0.64	0.72 (0.55 to 0.93)	0.01	0.53 (0.35 to 0.80)	< 0.01
4	0.69 (0.55 to 0.85)	< 0.01	0.58 (0.46 to 0.74)	< 0.01	0.63 (0.43 to 0.90)	0.01
5	0.74 (0.59 to 0.93)	0.01	0.54 (0.42 to 0.70)	< 0.01	0.63 (0.43 to 0.92)	0.02

continued

TABLE 40 Adjusted ORs for the association between patient characteristics and sleep disturbance treatment (*continued*)

Characteristic	Z-drug		Low-dose TCA		BZD	
	OR[a] (95% CI)	*p*-value	OR[a] (95% CI)	*p*-value	OR[a] (95% CI)	*p*-value
Smoking status						
Non-smoker	1.00		1.00		1.00	
Ex-smoker	0.97 (0.82 to 1.13)	0.66	1.10 (0.93 to 1.31)	0.27	1.05 (0.79 to 1.39)	0.75
Current smoker	1.26 (0.99 to 1.60)	0.06	1.10 (0.83 to 1.44)	0.51	1.14 (0.75 to 1.72)	0.55
Missing	0.83 (0.53 to 1.32)	0.44	0.60 (0.35 to 1.02)	0.06	0.45 (0.22 to 0.95)	0.04
Alcohol user						
No	1.00		1.00		1.00	
Yes	0.80 (0.68 to 0.93)	< 0.01	0.83 (0.70 to 0.99)	0.03	0.79 (0.59 to 1.05)	0.10
Missing	1.53 (1.12 to 2.11)	0.01	1.79 (1.27 to 2.53)	< 0.01	1.33 (0.81 to 2.18)	0.27
BMI (kg/m^2)						
< 18.5	1.00		1.00		1.00	
18.5–24.9	1.04 (0.78 to 1.38)	0.80	1.02 (0.74 to 1.41)	0.89	0.64 (0.38 to 1.10)	0.11
25–29.9	1.06 (0.78 to 1.43)	0.73	1.17 (0.84 to 1.65)	0.36	0.87 (0.49 to 1.52)	0.62
≥ 30	1.30 (0.92 to 1.84)	0.14	1.21 (0.82 to 1.78)	0.34	0.93 (0.48 to 1.80)	0.83
Missing	1.36 (1.01 to 1.83)	0.05	1.29 (0.92 to 1.81)	0.14	1.59 (0.94 to 2.68)	0.08
Systolic blood pressure (mmHg)						
< 110	1.00		1.00		1.00	
110–119	1.18 (0.87 to 1.60)	0.28	1.50 (1.05 to 2.13)	0.03	1.13 (0.68 to 1.88)	0.64
120–139	1.12 (0.86 to 1.45)	0.40	1.39 (1.03 to 1.88)	0.03	0.80 (0.52 to 1.24)	0.32
140–159	1.20 (0.92 to 1.57)	0.17	1.45 (1.06 to 1.99)	0.02	1.03 (0.66 to 1.62)	0.89
≥ 160	1.31 (0.95 to 1.80)	0.11	1.69 (1.17 to 2.45)	0.01	1.20 (0.70 to 2.04)	0.51
Missing	1.71 (0.99 to 2.93)	0.05	2.87 (1.56 to 5.29)	< 0.01	1.86 (0.88 to 3.94)	0.11
Dementia						
Anticholinesterase/ memantine prescription × in last 90 days	1.29 (1.10 to 1.52)	< 0.01	1.26 (1.05 to 1.50)	0.01	1.19 (0.88 to 1.61)	0.26
Antipsychotic prescription in last 90 days	1.31 (1.10 to 1.56)	< 0.01	0.81 (0.66 to 1.00)	0.05	0.78 (0.57 to 1.07)	0.12
Agitation/psychosis history	0.64 (0.54 to 0.75)	< 0.01	0.72 (0.60 to 0.87)	< 0.01	1.35 (1.03 to 1.77)	0.03
End-of-life care	0.89 (0.65 to 1.21)	0.45	0.90 (0.64 to 1.26)	0.53	1.52 (0.91 to 2.54)	0.11
Sleep disturbance						
Sleep disturbance diagnosis pre dementia	0.58 (0.50 to 0.68)	< 0.01	0.45 (0.37 to 0.54)	< 0.01	0.46 (0.33 to 0.64)	< 0.01
History of BZD use	1.63 (1.38 to 1.93)	< 0.01	1.65 (1.37 to 1.99)	< 0.01	1.95 (1.44 to 2.64)	< 0.01
History of Z-drug use	1.83 (1.39 to 2.40)	< 0.01	1.15 (0.84 to 1.58)	0.39	1.21 (0.69 to 2.11)	0.51
Medical history in past year						
Falls	0.77 (0.66 to 0.91)	< 0.01	0.65 (0.54 to 0.78)	< 0.01	0.86 (0.65 to 1.14)	0.30
Fractures	1.44 (1.11 to 1.86)	0.01	1.08 (0.80 to 1.44)	0.62	1.00 (0.63 to 1.59)	0.99
Influenza vaccination	0.93 (0.81 to 1.07)	0.33	1.17 (0.99 to 1.38)	0.06	1.16 (0.90 to 1.50)	0.24
Pneumonia vaccination	0.91 (0.69 to 1.21)	0.53	0.79 (0.56 to 1.09)	0.15	0.46 (0.26 to 0.83)	0.01

TABLE 40 Adjusted ORs for the association between patient characteristics and sleep disturbance treatment (*continued*)

	Z-drug		Low-dose TCA		BZD	
Characteristic	OR[a] (95% CI)	*p*-value	OR[a] (95% CI)	*p*-value	OR[a] (95% CI)	*p*-value
GP consultations						
0–3	1.00		1.00		1.00	
4–5	1.00 (0.82 to 1.21)	0.97	1.24 (0.99 to 1.54)	0.06	1.11 (0.79 to 1.56)	0.55
6–8	1.13 (0.93 to 1.36)	0.21	1.37 (1.10 to 1.69)	< 0.01	1.27 (0.91 to 1.77)	0.16
9–13	1.05 (0.86 to 1.27)	0.63	1.40 (1.13 to 1.74)	< 0.01	1.05 (0.75 to 1.49)	0.77
14–77	1.28 (1.03 to 1.59)	0.03	1.57 (1.23 to 2.00)	< 0.01	1.15 (0.77 to 1.70)	0.49
Hospital admissions						
0	1.00		1.00		1.00	
1	1.48 (1.26 to 1.74)	< 0.01	1.31 (1.09 to 1.56)	< 0.01	1.39 (1.05 to 1.84)	0.02
≥ 2	1.92 (1.61 to 2.30)	< 0.01	1.51 (1.23 to 1.84)	< 0.01	1.59 (1.16 to 2.16)	< 0.01
Comorbidities						
ARMD	0.97 (0.74 to 1.27)	0.82	1.34 (1.00 to 1.78)	0.05	1.42 (0.90 to 2.25)	0.13
Back/neck pain	0.97 (0.84 to 1.11)	0.62	1.17 (1.00 to 1.36)	0.05	0.59 (0.46 to 0.76)	< 0.01
Migraine/headache	1.00 (0.85 to 1.18)	0.98	1.27 (1.06 to 1.52)	0.01	0.65 (0.45 to 0.92)	0.02
Depression symptoms	0.83 (0.70 to 1.00)	0.05	1.09 (0.90 to 1.32)	0.37	0.76 (0.54 to 1.09)	0.14
Hypertension	0.83 (0.72 to 0.95)	0.01	0.93 (0.80 to 1.09)	0.37	0.61 (0.48 to 0.79)	< 0.01
Heart failure	0.82 (0.65 to 1.03)	0.08	0.74 (0.57 to 0.96)	0.02	0.63 (0.40 to 1.00)	0.05
Osteoporosis	0.91 (0.73 to 1.14)	0.43	0.95 (0.74 to 1.21)	0.67	1.62 (1.10 to 2.40)	0.02
Other joint conditions	0.72 (0.61 to 0.85)	< 0.01	0.79 (0.65 to 0.96)	0.02	0.31 (0.24 to 0.41)	< 0.01
Other musculoskeletal conditions	1.02 (0.84 to 1.24)	0.85	1.01 (0.82 to 1.25)	0.94	1.50 (1.09 to 2.08)	0.01
Parkinson's disease	0.89 (0.68 to 1.17)	0.41	0.57 (0.41 to 0.79)	< 0.01	0.66 (0.39 to 1.11)	0.12
Urinary incontinence	0.52 (0.44 to 0.61)	< 0.01	0.67 (0.56 to 0.81)	< 0.01	0.72 (0.53 to 0.98)	0.04
Prescriptions in last 90 days						
ACE inhibitor	1.04 (0.88 to 1.23)	0.65	1.15 (0.96 to 1.38)	0.13	1.39 (1.04 to 1.88)	0.03
Analgesic	1.29 (1.13 to 1.49)	< 0.01	2.09 (1.79 to 2.44)	< 0.01	1.24 (0.97 to 1.58)	0.09
Antiepileptic	0.97 (0.73 to 1.28)	0.81	1.12 (0.83 to 1.50)	0.46	3.70 (2.57 to 5.34)	< 0.01
Antihistamine	0.76 (0.53 to 1.09)	0.13	0.98 (0.67 to 1.42)	0.91	1.48 (0.84 to 2.61)	0.17
Beta-blocker	1.10 (0.92 to 1.31)	0.30	0.91 (0.75 to 1.10)	0.33	1.18 (0.86 to 1.62)	0.31
Bisphosphonate	0.98 (0.77 to 1.26)	0.89	1.32 (1.01 to 1.71)	0.04	0.83 (0.52 to 1.32)	0.43
NSAID	1.22 (0.94 to 1.59)	0.14	1.73 (1.32 to 2.27)	< 0.01	1.95 (1.29 to 2.94)	< 0.01
SSRI	1.17 (0.99 to 1.39)	0.07	0.80 (0.66 to 0.98)	0.03	0.95 (0.69 to 1.29)	0.73
Other antidepressant	0.79 (0.61 to 1.02)	0.08	0.52 (0.38 to 0.70)	< 0.01	0.78 (0.49 to 1.25)	0.30
Antibiotic (in last 30 days)	1.18 (1.00 to 1.40)	0.05	1.00 (0.83 to 1.21)	0.97	1.01 (0.75 to 1.36)	0.93

ACE, angiotensin-converting enzyme.
a Adjusted for all covariates in the table.

Appendix 3 Additional REDIC study analyses

TABLE 41 Distribution, autocorrelation and pairwise Spearman correlations of neuropsychiatric measures included in the current study

					Measure										
					NPI						CSDD				
Measure	Number missing (%)	None, *n* (%)	Mild/ moderate, *n* (%)	Severe, *n* (%)	Anxiety total	Agitation total	Sleep total	Anxiety distress	Agitation distress	Sleep distress	Agitation	Anxiety	Difficulty falling asleep	Frequent waking	Waking early
NPI															
Anxiety total	81 (4)	1344 (63)	498 (23)	295 (14)	0.52										
Agitation total	82 (4)	1448 (68)	456 (21)	232 (11)	0.21	0.55									
Sleep total	82 (4)	1637 (77)	322 (15)	177 (8)	0.17	0.21	0.46								
Anxiety distress	356 (16)	1197 (64)	402 (22)	263 (14)	0.87	0.25	0.19	0.53							
Agitation distress	376 (17)	1212 (66)	297 (16)	333 (18)	0.23	0.91	0.23	0.30	0.64						
Sleep distress	463 (21)	1278 (73)	252 (14)	216 (12)	0.17	0.23	0.91	0.21	0.26	0.52					
CSDD															
Agitation	33 (1)	1700 (78)	319 (15)	166 (8)	0.29	0.41	0.18	0.33	0.43	0.21	0.47				
Anxiety	51 (2)	787 (36)	949 (44)	431 (20)	0.53	0.20	0.18	0.50	0.20	0.18	0.32	0.51			
Difficulty falling asleep	59 (3)	1826 (85)	243 (11)	90 (4)	0.17	0.08	0.31	0.15	0.11	0.29	0.13	0.18	0.29		
Frequent waking	68 (3)	1487 (69)	487 (23)	176 (8)	0.19	0.10	0.59	0.18	0.11	0.55	0.14	0.21	0.44	0.38	
Waking early	54 (2)	1889 (88)	197 (9)	78 (4)	0.17	0.10	0.25	0.15	0.08	0.23	0.15	0.17	0.33	0.38	0.21

Notes
For illustration, NPI-NH 'total' variables are recoded from the product of 'severity' and 'frequency' variables ('none' = 0, 'mild/moderate' = 1–4, 'severe' = 6–12). Distress variables as coded as 'none' = 0, 'mild/moderate' = 1–2, 'severe' = 3–5.
CSDD variables are coded as initially recorded.
Diagonals of the correlation matrix show the Spearman's correlation coefficient between current and previous assessments among participants. Off-diagonal elements show correlation between concurrent values of each pair of variables.
Correlations between 0.3 and 0.8 are shaded in light green, correlations > 0.8 are shaded in dark green.

TABLE 42 The number and proportion of the sample who provided assessments at each follow-up interview, and the proportion of those assessed who were using each class of medication at each visit

Visit	Assessed, *n* (%)	Z-drugs, *n* (%)	BZD, *n* (%)	Antipsychotics, *n* (%)	Antihistamines, *n* (%)	Antidepressants, *n* (%)	Antiepileptics, *n* (%)
1 (baseline)	678 (100.0)	126 (18.6)	107 (15.8)	84 (12.4)	26 (3.8)	196 (28.9)	37 (5.5)
2 (6 months)	496 (73.2)	106 (21.4)	97 (19.6)	85 (17.1)	23 (4.6)	193 (38.9)	33 (6.7)
3 (12 months)	417 (61.5)	74 (17.7)	93 (22.3)	66 (15.8)	18 (4.3)	169 (40.5)	26 (6.2)
4 (18 months)	341 (50.3)	62 (18.2)	83 (24.3)	68 (19.9)	19 (5.6)	135 (39.6)	29 (8.5)
5 (24 months)	286 (42.2)	53 (18.5)	60 (21.0)	46 (16.1)	12 (4.2)	119 (41.6)	24 (8.4)

TABLE 43 Multiple logistic regression showing the association between clinical and demographic factors and dropout before the next REDIC study visit

	OR (drop out at next wave)	95% CI
Hypnotic use		
BZD	0.64*	0.44 to 0.92
Z-drug	1.47*	1.03 to 2.09
Antipsychotic	0.88	0.60 to 1.29
Age (years)		
< 70	0.54	0.22 to 1.32
70–79	1	1.00 to 1.00
80–89	1.47	0.96 to 2.26
≥ 90	1.63*	1.03 to 2.59
Dementia severity		
Minimal	1.06	0.62 to 1.81
Mild	1.15	0.78 to 1.70
Moderate	0.61**	0.43 to 0.86
Severe	1	1.00 to 1.00
Sex: female (vs. male)	1.13	0.84 to 1.53
Marital status		
Unmarried	1	1.00 to 1.00
Married	1.01	0.59 to 1.73
Widowed/divorced	1	0.59 to 1.69
Neuropsychiatric symptoms		
Sleep	1.12	0.96 to 1.31
Anxiety	1.22	0.98 to 1.51
Agitation	0.76	0.56 to 1.03
Disability (Lawton Physical Self-Maintenance Scale), per unit	1.12***	1.08 to 1.15
Years in education		
< 7	0.82	0.39 to 1.74
7	0.70*	0.49 to 1.00
8–11	0.77	0.55 to 1.09
≥ 12	1	1.00 to 1.00
Type of admission		
Long stay	1	1.00 to 1.00
Short stay	1.52*	1.07 to 2.15
Nursing	1.08	0.59 to 1.99

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Note

Neuropsychiatric symptoms are coded as factor scores combining NPI-NH and CSDD assessments.

TABLE 44 Association between clinical and demographic factors and continuing to use hypnotics at the next visit, among those who report use at the current visit

	Continuing Z-drugs		Continuing BZDs		Continuing antipsychotics	
	OR	95% CI	OR	95% CI	OR	95% CI
Age (years)						
< 70	3.1	0.24 to 40.08	0.99	0.14 to 7.12	2.36	0.41 to 13.48
70–79	Ref		Ref		Ref	
80–89	0.66	0.28 to 1.57	1.26	0.50 to 3.17	0.79	0.32 to 1.96
≥ 90	1.11	0.37 to 3.33	0.71	0.23 to 2.19	0.73	0.22 to 2.47
Dementia severity						
Minimal	1.75	0.62 to 4.98	1.68	0.47 to 6.03	0.57	0.14 to 2.33
Mild	0.93	0.37 to 2.37	0.97	0.32 to 2.94	1.91	0.54 to 6.79
Moderate	1.9	0.81 to 4.48	1.06	0.43 to 2.57	1.24	0.52 to 2.96
Severe	Ref		Ref		Ref	
Sex: female (vs. male)	0.9	0.34 to 2.37	0.93	0.45 to 1.92	0.54	0.23 to 1.26
Marital status						
Unmarried	Ref		Ref		Ref	
Married	1.02	0.21 to 4.92	0.3	0.06 to 1.46	1.38	0.48 to 3.93
Widowed/divorced	0.91	0.19 to 4.29	0.4	0.10 to 1.68	0.61	0.23 to 1.62
Hypnotic use						
BZDs	2.02	0.97 to 4.20			1.19	0.58 to 2.43
Z-drugs			1.49	0.72 to 3.11	1.19	0.47 to 2.98
Antipsychotics	0.8	0.38 to 1.68	1.79	0.81 to 3.97		
Neuropsychiatric symptoms						
Sleep	0.88	0.58 to 1.34	0.88	0.60 to 1.29	0.89	0.59 to 1.34
Anxiety	0.98	0.59 to 1.61	0.87	0.50 to 1.50	1.15	0.66 to 1.98
Agitation	0.75	0.35 to 1.61	1.31	0.70 to 2.47	0.95	0.46 to 1.96
Disability (Lawton Physical Self-Maintenance Scale), per unit	0.95	0.88 to 1.03	1.03	0.96 to 1.12	0.97	0.89 to 1.06
Years in education						
< 7	3.92	0.55 to 28.12	1.66	0.20 to 14.06	0.35	0.04 to 3.18
7	1.67	0.63 to 4.42	0.32**	0.13 to 0.76	0.65	0.25 to 1.64
8–11	1.8	0.78 to 4.20	0.85	0.37 to 1.95	0.5	0.22 to 1.17
≥ 12	Ref		Ref		Ref	
Type of admission						
Long stay	Ref		Ref		Ref	
Short stay	0.81	0.32 to 2.03	0.56	0.26 to 1.22	1.31	0.49 to 3.49
Nursing	1.59	0.14 to 17.81	0.46	0.12 to 1.75	0.66	0.02 to 20.89

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
Ref, reference.

TABLE 45 Association between hypnotic use status and change in outcome at previous and current visits, estimated using modelling approaches (described fully in text)

Outcome	Exposure	Estimate of effect, β (95% CI)			
		Marginal structural model	Fixed effects model 1 (all participants)	Fixed effects model 2 (new users)	Fixed effects model 3 (mild dementia)
Sleep disturbance	Z-drugs	0.20 (–0.02 to 0.43)	–0.01 (–0.15 to 0.13)	–0.13 (–0.38 to 0.11)	0.25 (–0.02 to 0.52)
	BZDs	–0.08 (–0.43 to 0.28)	–0.01 (–0.15 to 0.12)	–0.02 (–0.24 to 0.20)	0.03 (–0.25 to 0.32)
	Antipsychotics	0.05 (–0.21 to 0.31)	–0.08 (–0.24 to 0.08)	–0.10 (–0.35 to 0.14)	0.21 (–0.28 to 0.70)
Agitation	Z-drugs	0.01 (–0.17 to 0.19)	0.07 (–0.01 to 0.16)	0.25*** (0.11 to 0.40)	0.11 (–0.05 to 0.28)
	BZDs	0.11* (0.00 to 0.21)	–0.02 (–0.11 to 0.06)	0.04 (–0.08 to 0.17)	0.07 (–0.09 to 0.24)
	Antipsychotics	0.13* (0.01 to 0.26)	0.07 (–0.02 to 0.16)	0.13 (–0.02 to 0.27)	0.00 (–0.29 to 0.29)
Anxiety	Z-drugs	0.04 (–0.09 to 0.17)	0.01 (–0.09 to 0.12)	0.00 (–0.18 to 0.18)	0.03 (–0.17 to 0.24)
	BZDs	0.09 (–0.06 to 0.24)	0.04 (–0.06 to 0.14)	0.05 (–0.10 to 0.21)	0.13 (–0.08 to 0.35)
	Antipsychotics	0.32** (0.12 to 0.51)	0.11 (0.00 to 0.23)	0.21* (0.03 to 0.39)	0.22 (–0.15 to 0.59)
QUALID	Z-drugs	0.18 (–1.46 to 1.82)	1.01* (0.06 to 1.96)	0.44 (–1.09 to 1.97)	0.74 (–1.03 to 2.51)
	BZDs	1.04 (–0.48 to 2.56)	0.49 (–0.43 to 1.42)	–0.47 (–1.85 to 0.91)	1.91* (0.18 to 3.65)
	Antipsychotics	1.63* (0.30 to 2.95)	1.21* (0.20 to 2.23)	1.20 (–0.27 to 2.66)	2.52 (–0.51 to 5.54)
EQ-5D (staff rated)	Z-drugs	–0.02 (–0.07 to 0.03)	–0.02 (–0.06 to 0.03)	–0.02 (–0.10 to 0.06)	–0.05 (–0.15 to 0.04)
	BZDs	–0.02 (–0.07 to 0.04)	0.00 (–0.05 to 0.05)	0.05 (–0.02 to 0.12)	0.00 (–0.09 to 0.09)
	Antipsychotics	–0.06 (–0.16 to 0.04)	–0.04 (–0.09 to 0.01)	–0.03 (–0.11 to 0.04)	–0.13 (–0.26 to 0.01)
VAS (staff rated)	Z-drugs	–5.37 (–12.76 to 2.03)	–6.76* (–12.73 to –0.79)	–3.88 (–14.80 to 7.04)	–1.11 (–14.62 to 12.41)
	BZDs	–4.33 (–15.73 to 7.06)	–2.00 (–8.58 to 4.59)	–1.74 (–12.08 to 8.59)	1.18 (–12.52 to 14.87)
	Antipsychotics	–5.91 (–13.72 to 1.89)	1.16 (–5.56 to 7.89)	–1.79 (–12.09 to 8.51)	2.82 (–14.78 to 20.42)

Outcome	Exposure	Estimate of effect, β (95% CI)			
		Marginal structural model	Fixed effects model 1 (all participants)	Fixed effects model 2 (new users)	Fixed effects model 3 (mild dementia)
MMSE	Z-drugs	–0.43 (–1.91 to 1.05)	0.10 (–0.78 to 0.99)	–0.16 (–1.63 to 1.30)	–1.20 (–3.50 to 1.10)
	BZDs	0.28 (–1.06 to 1.61)	–0.55 (–1.42 to 0.32)	–0.82 (–2.16 to 0.51)	0.85 (–1.45 to 3.15)
	Antipsychotics	–0.44 (–1.56 to 0.68)	–0.33 (–1.29 to 0.62)	–0.11 (–1.53 to 1.30)	–0.91 (–4.91 to 3.10)
SIB-8	Z-drugs	–0.84 (–2.03 to 0.35)	0.33 (–0.38 to 1.04)	0.16 (–1.04 to 1.37)	–0.14 (–1.87 to 1.59)
	BZDs	0.43 (–0.55 to 1.41)	–0.14 (–0.84 to 0.56)	0.20 (–0.90 to 1.30)	0.37 (–1.36 to 2.09)
	Antipsychotics	–0.01 (–0.91 to 0.90)	0.05 (–0.71 to 0.81)	–0.27 (–1.44 to 0.90)	–0.39 (–3.40 to 2.61)
CDR	Z-drugs	0.51 (–0.16 to 1.18)	–0.10 (–0.53 to 0.34)	0.66 (–0.07 to 1.39)	–0.44 (–1.29 to 0.41)
	BZDs	0.69* (0.12 to 1.26)	0.52* (0.09 to 0.95)	0.71* (0.05 to 1.37)	0.39 (–0.45 to 1.23)
	Antipsychotics	0.53 (–0.19 to 1.25)	0.41 (–0.06 to 0.88)	0.31 (–0.40 to 1.01)	0.61 (–0.85 to 2.07)
Disability	Z-drugs	–0.07 (–0.75 to 0.60)	–0.17 (–0.69 to 0.35)	0.29 (–0.60 to 1.18)	–0.52 (–1.53 to 0.49)
	BZDs	0.08 (–0.60 to 0.75)	–0.11 (–0.62 to 0.40)	–0.07 (–0.88 to 0.74)	0.26 (–0.75 to 1.27)
	Antipsychotics	0.50 (–0.32 to 1.33)	0.74** (0.18 to 1.31)	0.56 (–0.30 to 1.42)	1.24 (–0.52 to 3.00)

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

TABLE 46 Association between patterns of hypnotic use and change in measures of agitation, anxiety and sleep disturbance between visits, adjusted for baseline age, baseline cognitive function and visit number

		β (95% CI)		
Exposure	Pattern	Agitation	Sleep	Anxiety
Z-drugs	No use	Ref	Ref	Ref
	Starting	0.09 (–0.06 to 0.25)	–0.27 (–0.58 to 0.03)	0.02 (–0.16 to 0.20)
	Stopping	–0.02 (–0.14 to 0.10)	–0.10 (–0.35 to 0.16)	0.03 (–0.13 to 0.20)
	Continuing	0.05 (–0.02 to 0.12)	–0.03 (–0.14 to 0.08)	0.00 (–0.09 to 0.08)
BZDs	No use	Ref	Ref	Ref
	Starting	0.04 (–0.13 to 0.21)	0.16 (–0.11 to 0.44)	0.01 (–0.18 to 0.19)
	Stopping	0.01 (–0.14 to 0.16)	0.24 (–0.02 to 0.50)	0.00 (–0.20 to 0.19)
	Continuing	–0.01 (–0.08 to 0.05)	–0.01 (–0.13 to 0.11)	0.05 (–0.04 to 0.14)
Antipsychotics	No use	Ref	Ref	Ref
	Starting	0.15 (–0.06 to 0.36)	0.02 (–0.27 to 0.31)	0.22 (–0.02 to 0.46)
	Stopping	0.15 (–0.03 to 0.32)	0.15 (–0.08 to 0.38)	0.12 (–0.10 to 0.34)
	Continuing	–0.10* (–0.19 to –0.01)	–0.10 (–0.24 to 0.05)	–0.01 (–0.13 to 0.12)

*$p < 0.05$.
Ref, reference.

TABLE 47 Association between patterns of hypnotic use and change in measures of QoL between visits, adjusted for baseline age, baseline cognitive function and visit number

	β (95% CI)		
Exposure	VAS	QUALID[a]	EQ-5D (staff)
Z-drugs			
No use	Ref	Ref	Ref
Starting	–7.13 (–16.88 to 2.61)	0.59 (–1.07 to 2.26)	–0.01 (–0.08 to 0.06)
Stopping	4.02 (–3.11 to 11.15)	–0.60 (–2.35 to 1.15)	0.06 (–0.01 to 0.13)
Continuing	4.04 (–0.56 to 8.64)	–0.17 (–0.94 to 0.60)	0.03 (–0.01 to 0.08)
BZDs			
No use	Ref	Ref	Ref
Starting	–0.67 (–12.81 to 11.48)	0.83 (–0.66 to 2.31)	0.05 (–0.02 to 0.12)
Stopping	7.38 (–7.13 to 21.89)	–0.97 (–2.60 to 0.66)	0.09* (0.01 to 0.16)
Continuing	–1.07 (–6.52 to 4.39)	–0.23 (–0.94 to 0.48)	0.03 (0.00 to 0.07)
Antipsychotics			
No use	Ref	Ref	Ref
Starting	–9.95* (–19.75 to –0.14)	1.66 (–0.19 to 3.50)	–0.03 (–0.10 to 0.05)
Stopping	–15.44*** (–24.03 to –6.85)	0.42 (–1.66 to 2.51)	–0.03 (–0.12 to 0.05)
Continuing	–5.96* (–11.74 to –0.17)	–0.01 (–0.98 to 0.96)	–0.01 (–0.05 to 0.04)

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
Ref, reference.
a For QUALID, higher scores correspond to lower QoL.

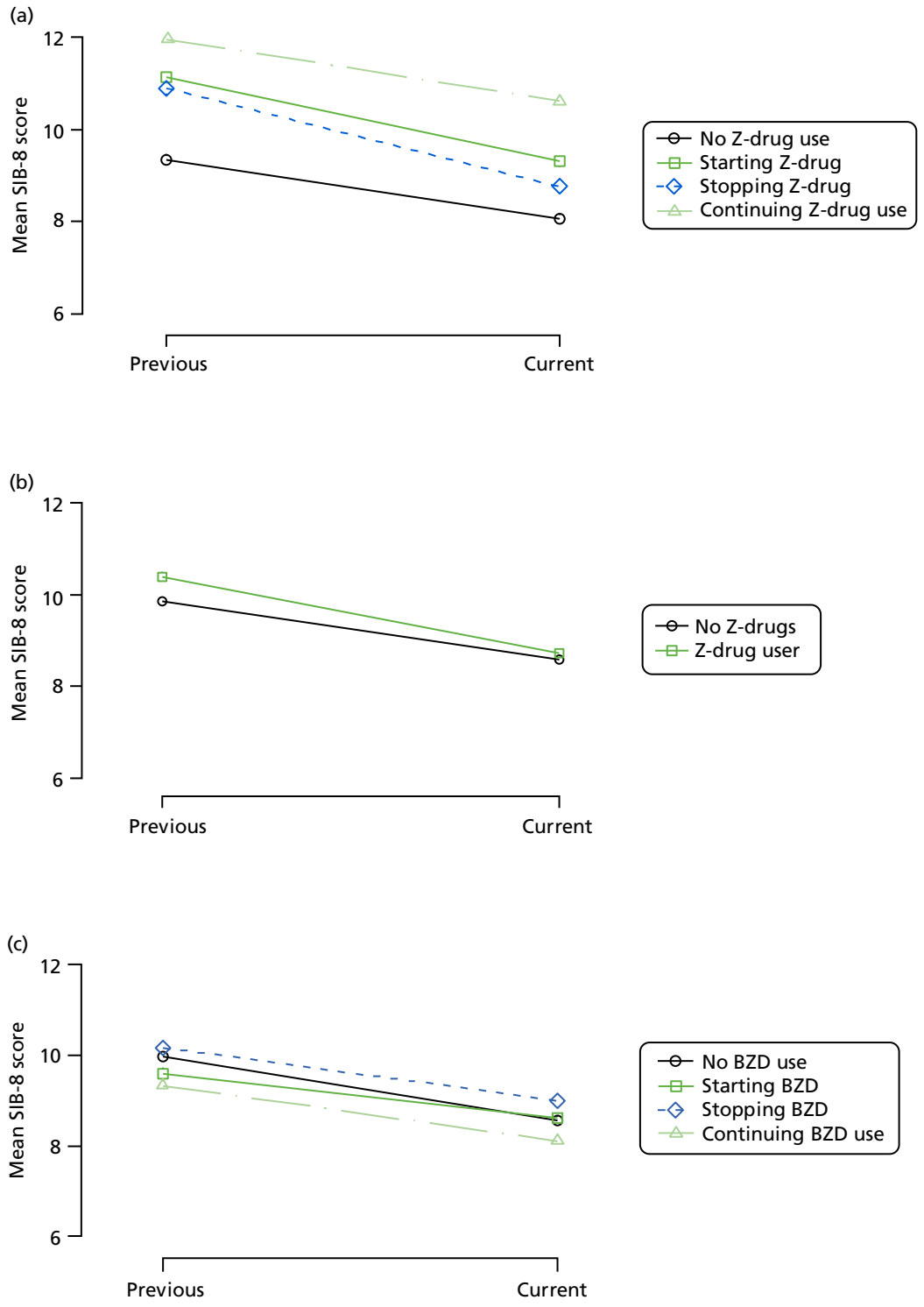

FIGURE 3 Association between changing hypnotic use status between previous and current visit on SIB-8 scores (higher scores represent better cognitive function) at previous and current visit (a, c and e). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (b, d and f). Data from the REDIC-NH study. AP, antipsychotic. (*continued*)

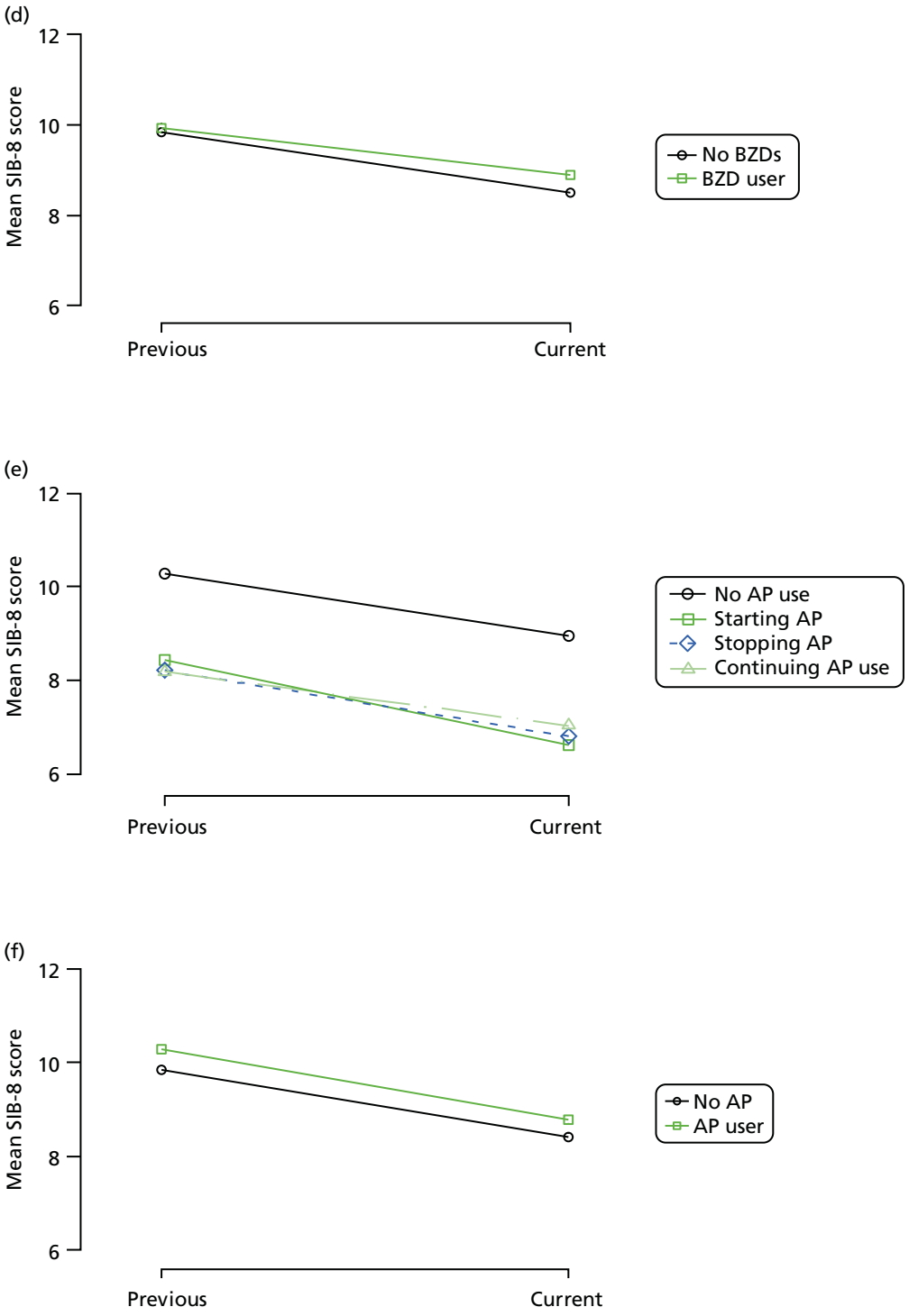

FIGURE 3 Association between changing hypnotic use status between previous and current visit on SIB-8 scores (higher scores represent better cognitive function) at previous and current visit (a, c and e). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (b, d and f). Data from the REDIC-NH study. AP, antipsychotic.

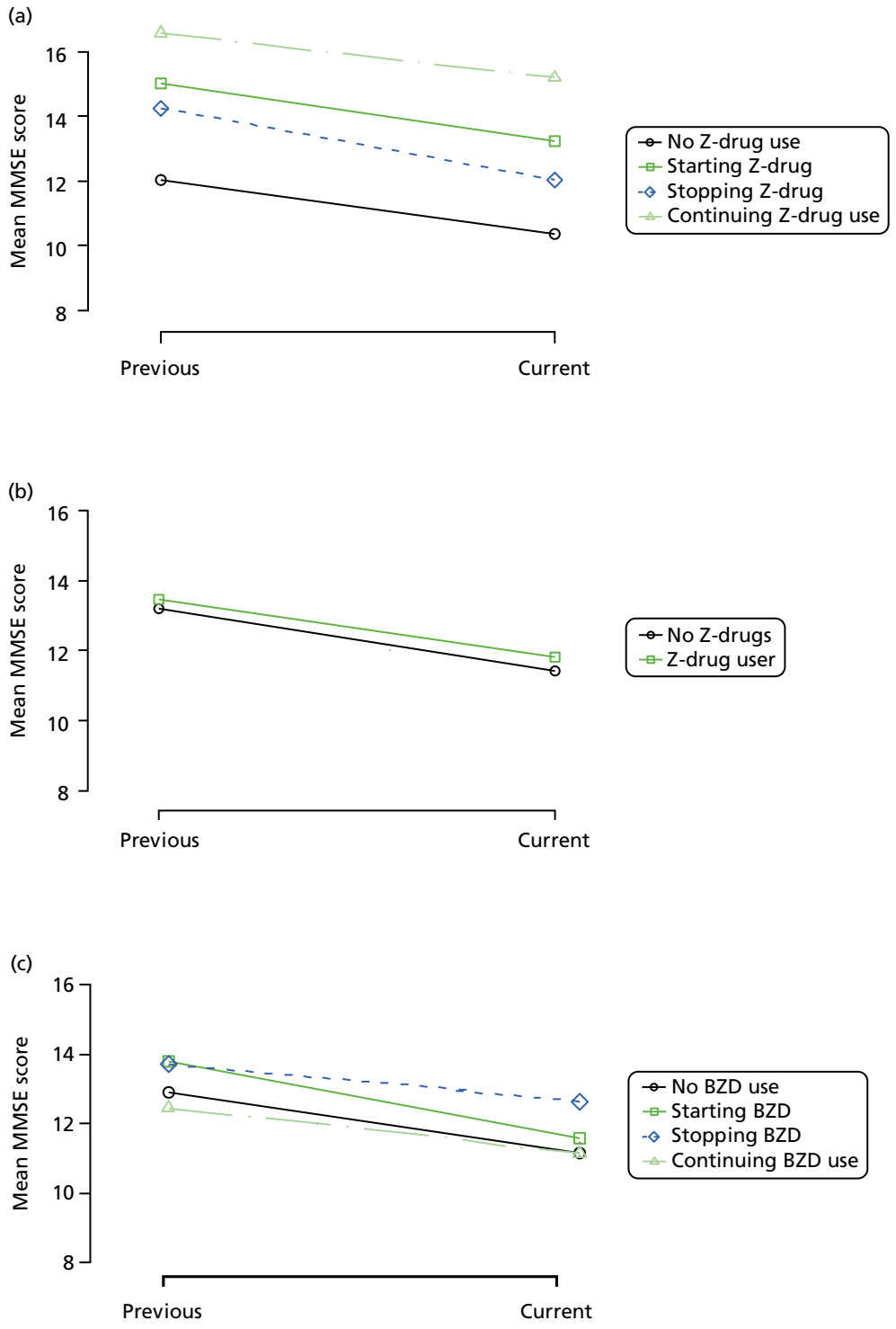

FIGURE 4 Association between changing hypnotic use status between previous and current visit on MMSE scores (higher scores represent better cognitive function) at previous and current visit (a, c and e). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (b, d and f). Data from the REDIC-NH study. AP, antipsychotic. (*continued*)

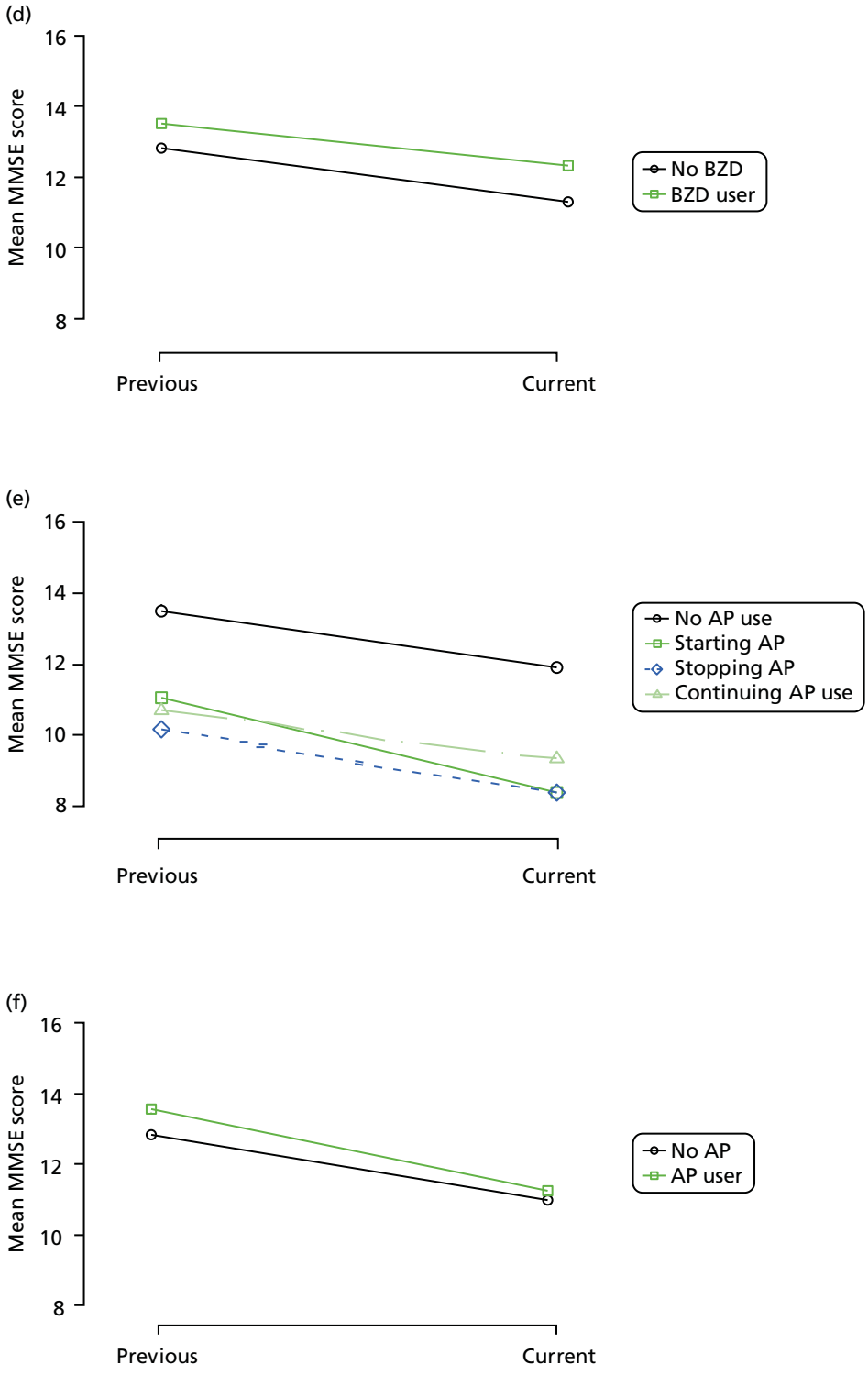

FIGURE 4 Association between changing hypnotic use status between previous and current visit on MMSE scores (higher scores represent better cognitive function) at previous and current visit (a, c and e). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (b, d and f). Data from the REDIC-NH study. AP, antipsychotic.

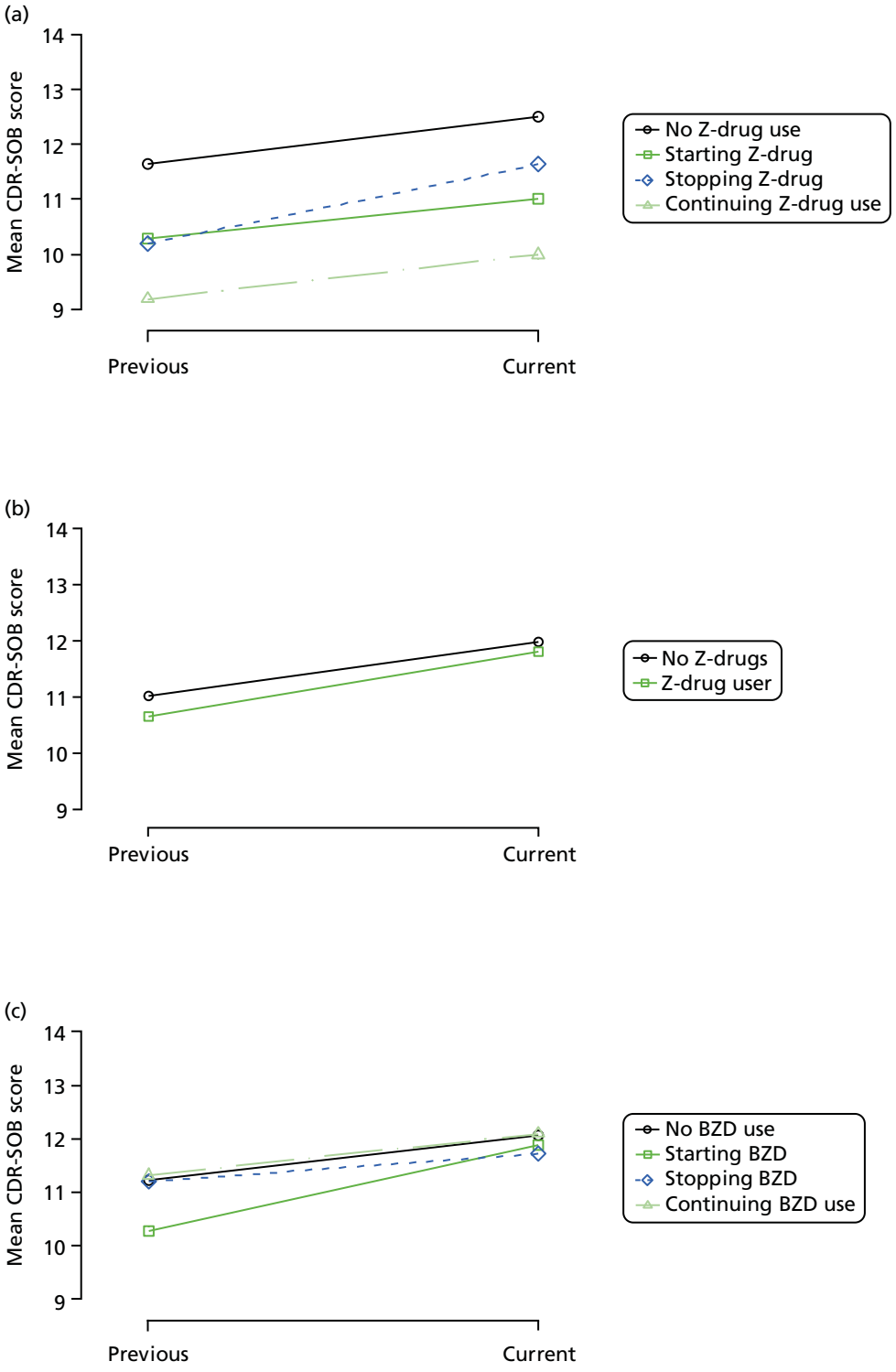

FIGURE 5 Association between changing hypnotic use status between previous and current visit on mean CDR-SOB scores (high scores represent more cognitive impairment) at previous and current visit (a, c and e). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (b, d and f). Data from the REDIC-NH study. AP, antipsychotic. (*continued*)

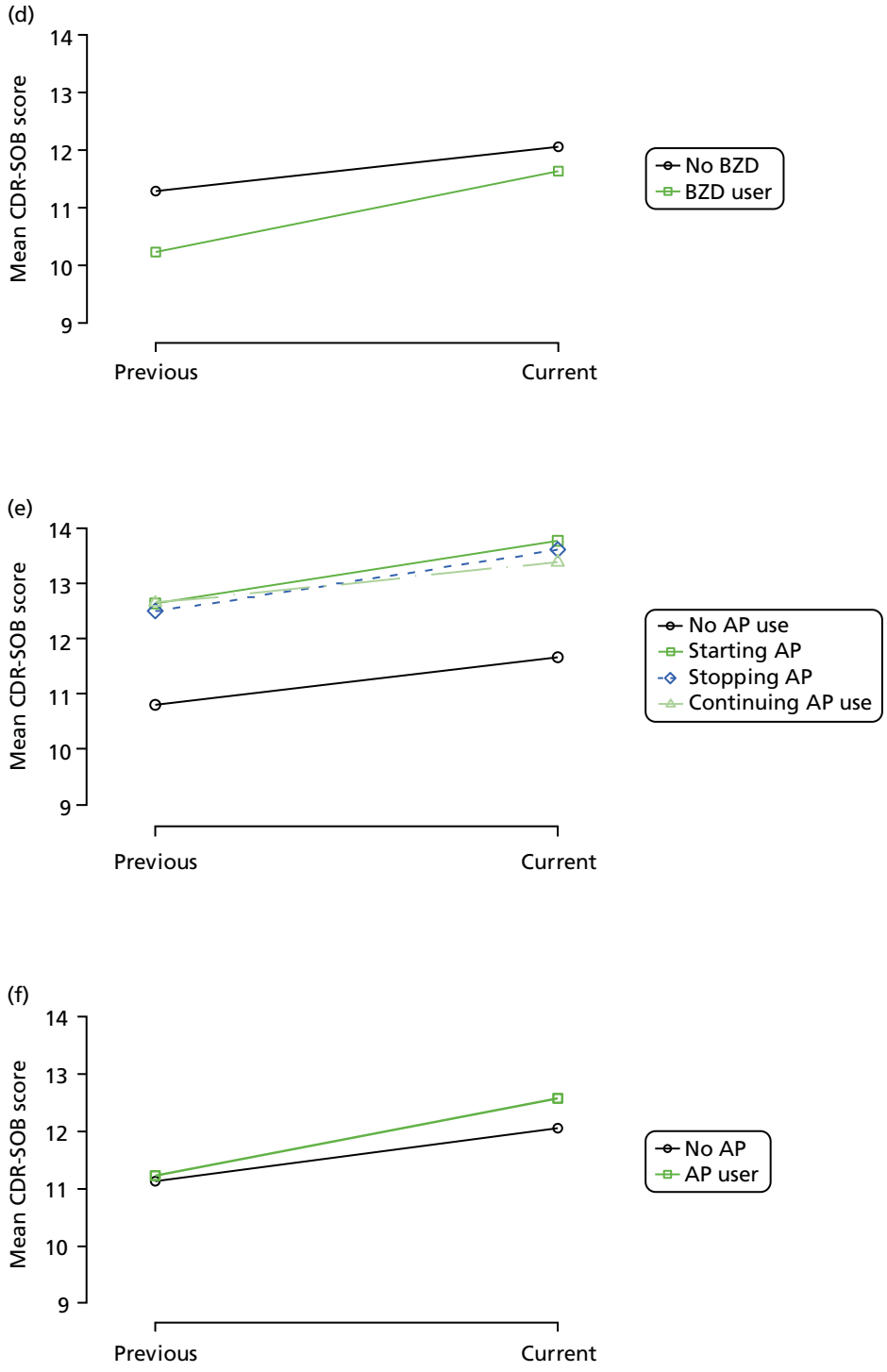

FIGURE 5 Association between changing hypnotic use status between previous and current visit on mean CDR-SOB scores (high scores represent more cognitive impairment) at previous and current visit (a, c and e). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (b, d and f). Data from the REDIC-NH study. AP, antipsychotic.

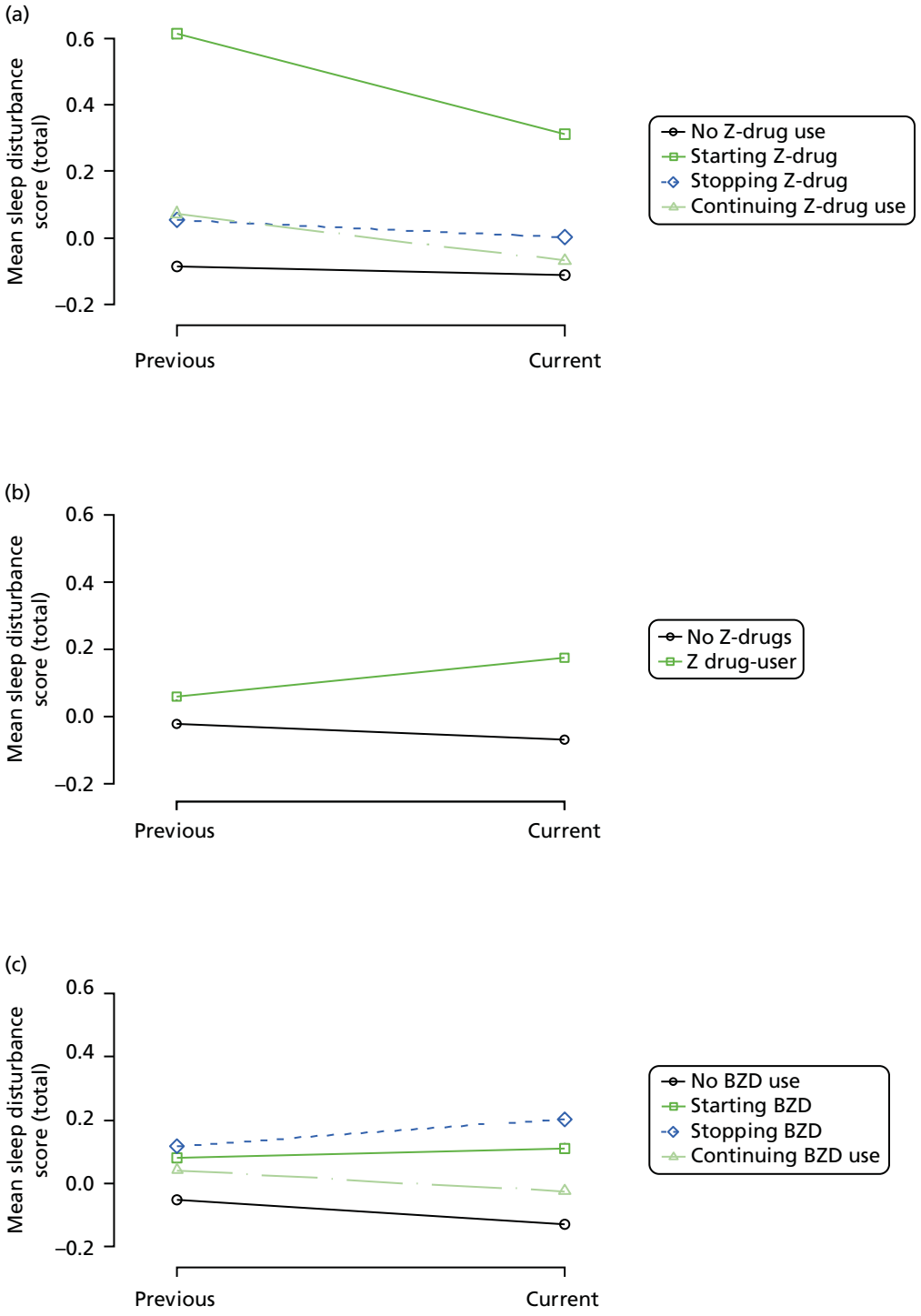

FIGURE 6 Association between changing hypnotic use status between previous and current visit on sleep disturbance scores at previous and current visit (a, c and e). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (b, d and f). Data from the REDIC-NH study. AP, antipsychotic. (*continued*)

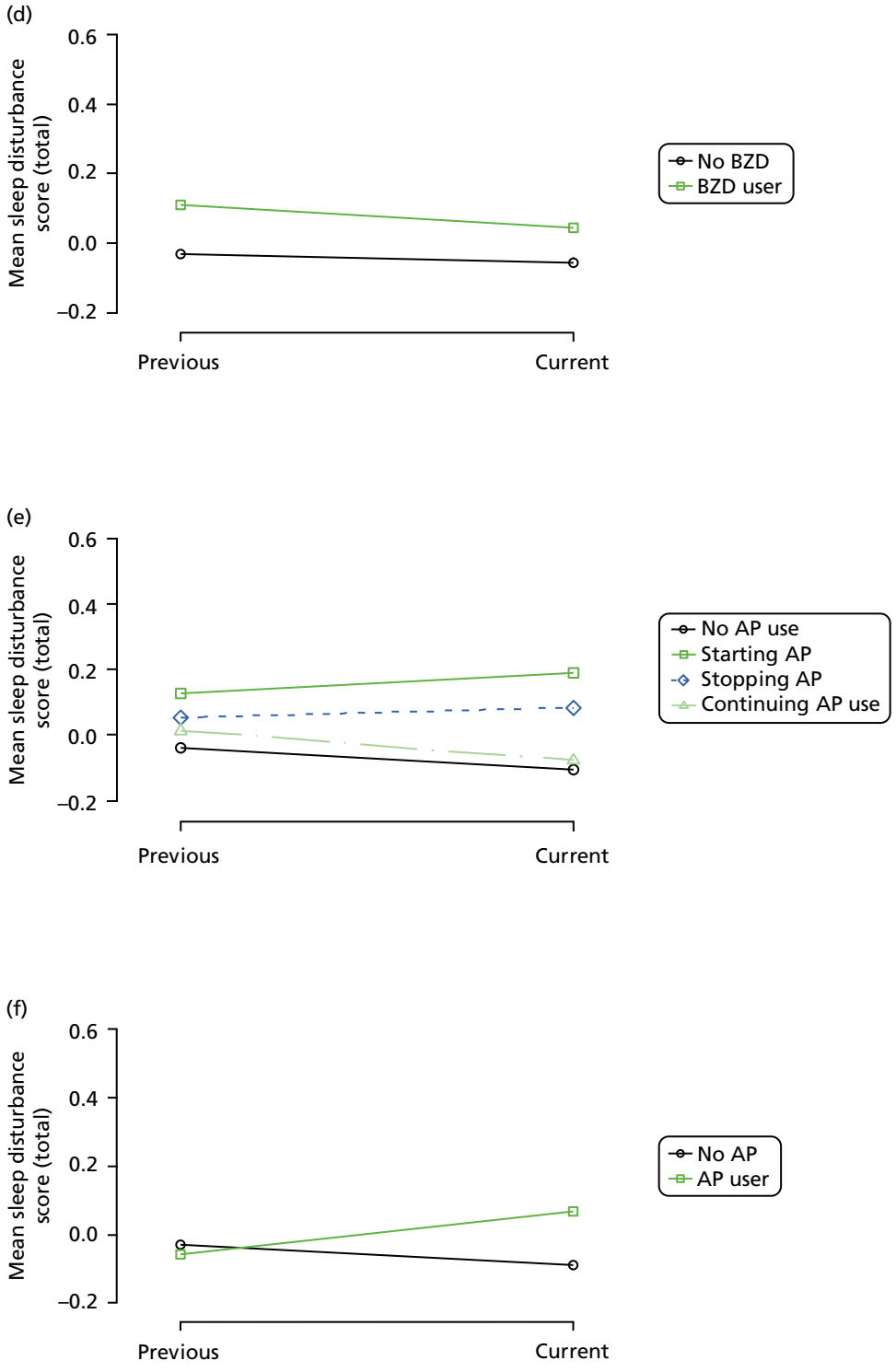

FIGURE 6 Association between changing hypnotic use status between previous and current visit on sleep disturbance scores at previous and current visit (a, c and e). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (b, d and f). Data from the REDIC-NH study. AP, antipsychotic.

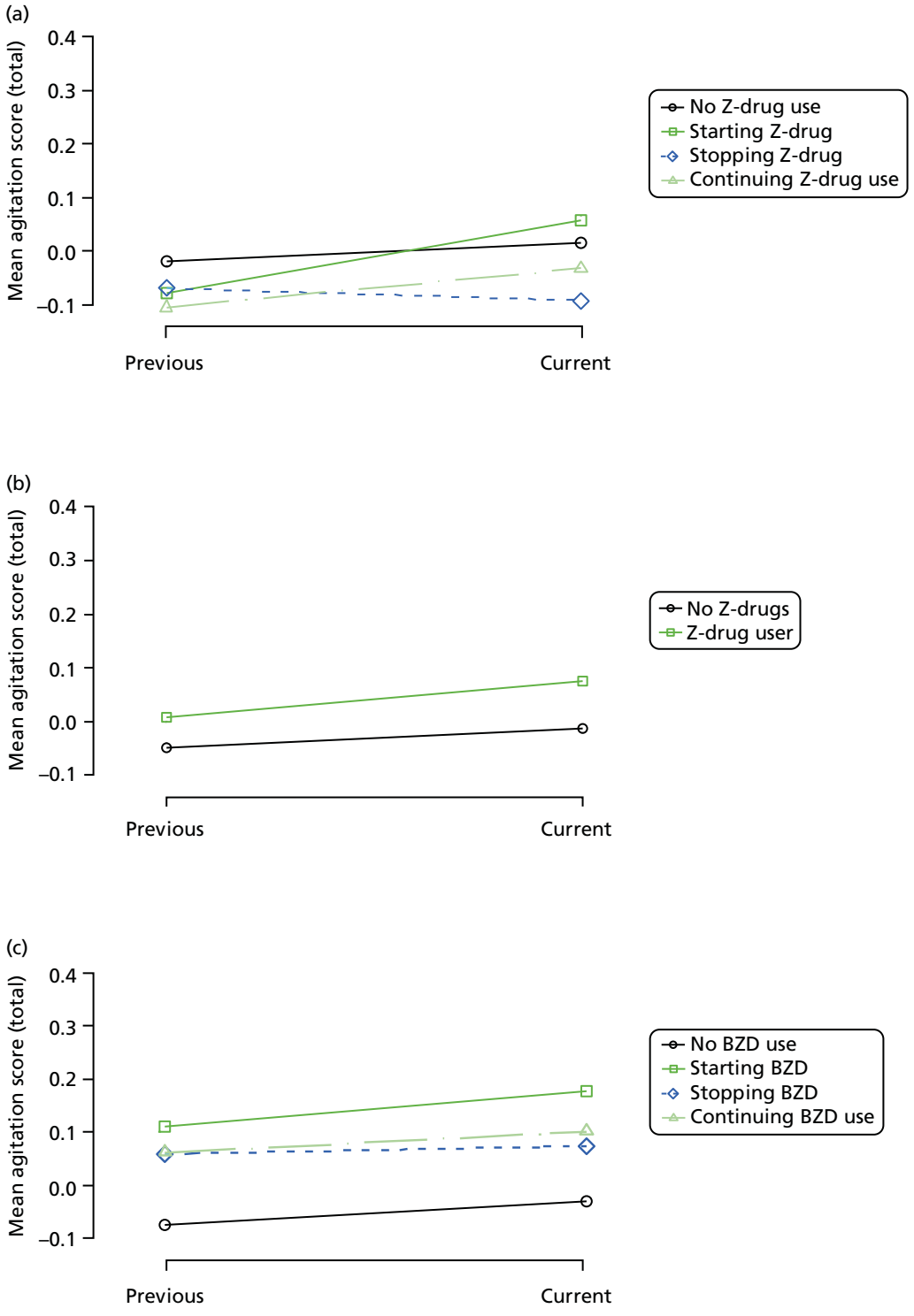

FIGURE 7 Association between changing hypnotic use status between previous and current visit on mean agitation scores at previous and current visit (a, c and e). Mean scores stratified by current hypnotic use, with inverse probability weights to account for differences in prior predictors of hypnotic use (b, d and f). Data from the REDIC-NH study. AP, antipsychotic. (*continued*)

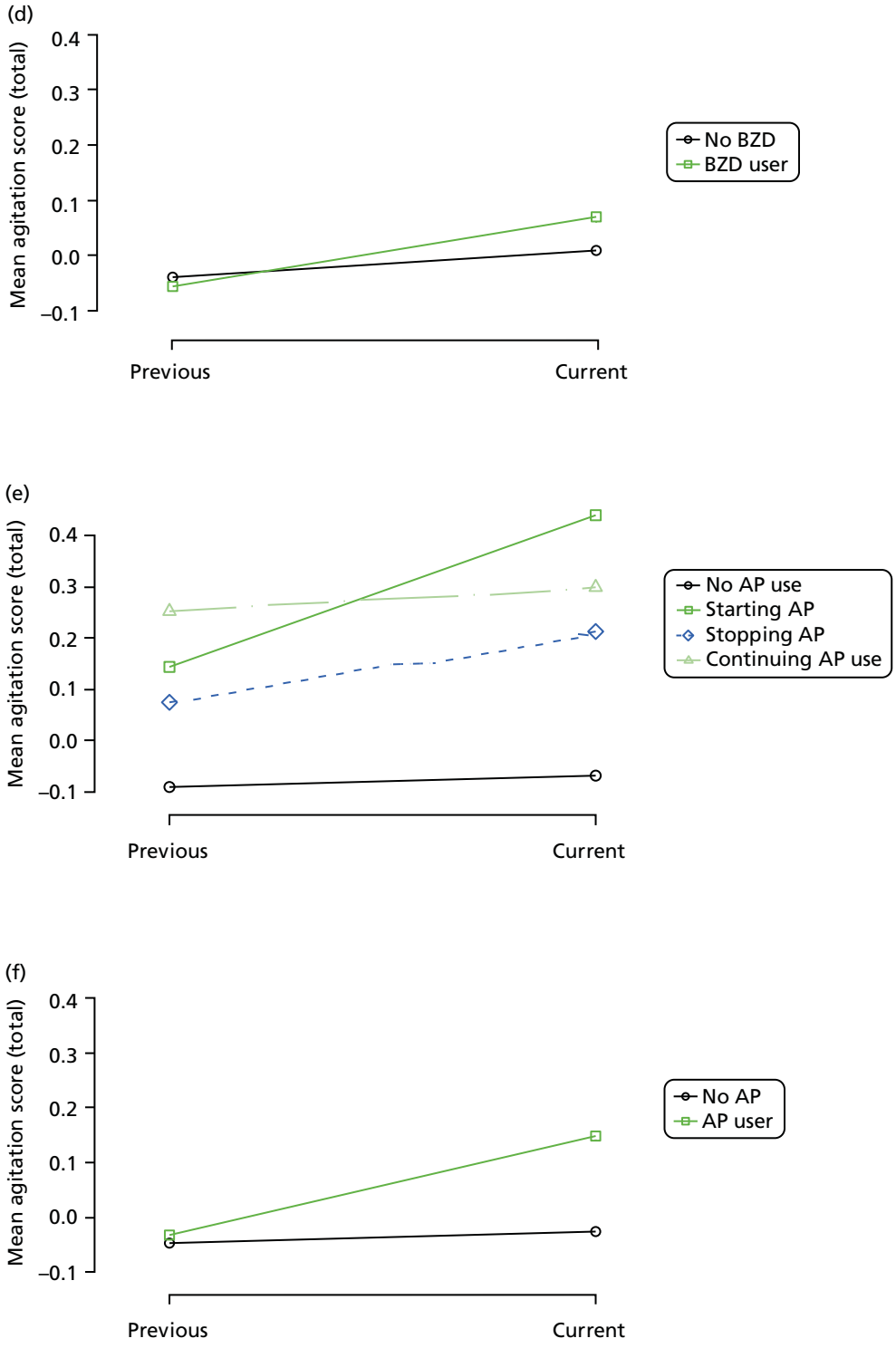

FIGURE 7 Association between changing hypnotic use status between previous and current visit on mean agitation scores at previous and current visit (a, c and e). Mean scores stratified by current hypnotic use, with inverse probability weights to account for differences in prior predictors of hypnotic use (b, d and f). Data from the REDIC-NH study. AP, antipsychotic.

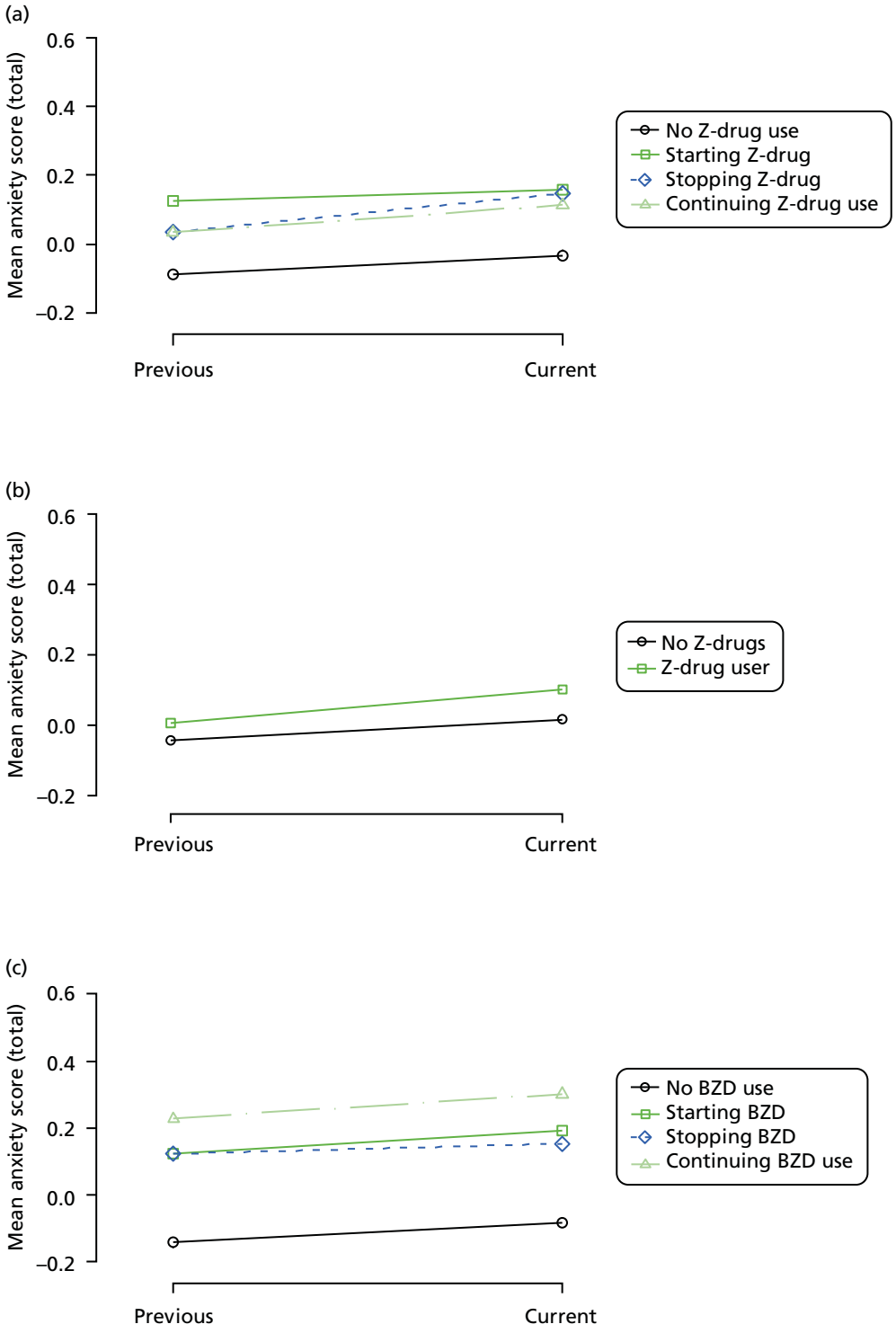

FIGURE 8 Association between changing hypnotic use status between previous and current visit on mean anxiety scores at previous and current visit (a, c and e). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (b, d and f). Data from the REDIC-NH study. AP, antipsychotic. (*continued*)

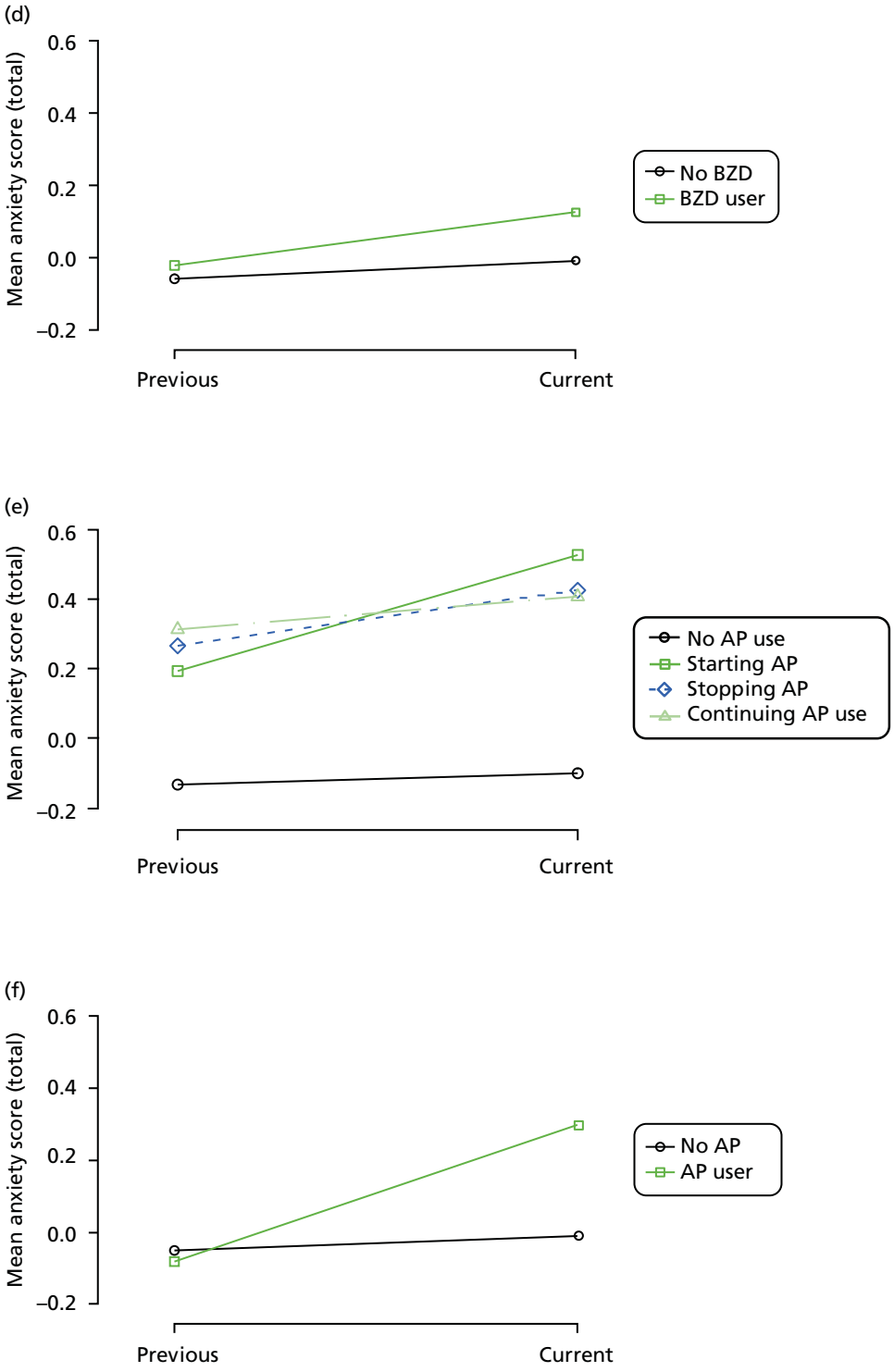

FIGURE 8 Association between changing hypnotic use status between previous and current visit on mean anxiety scores at previous and current visit (a, c and e). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (b, d and f). Data from the REDIC-NH study. AP, antipsychotic.

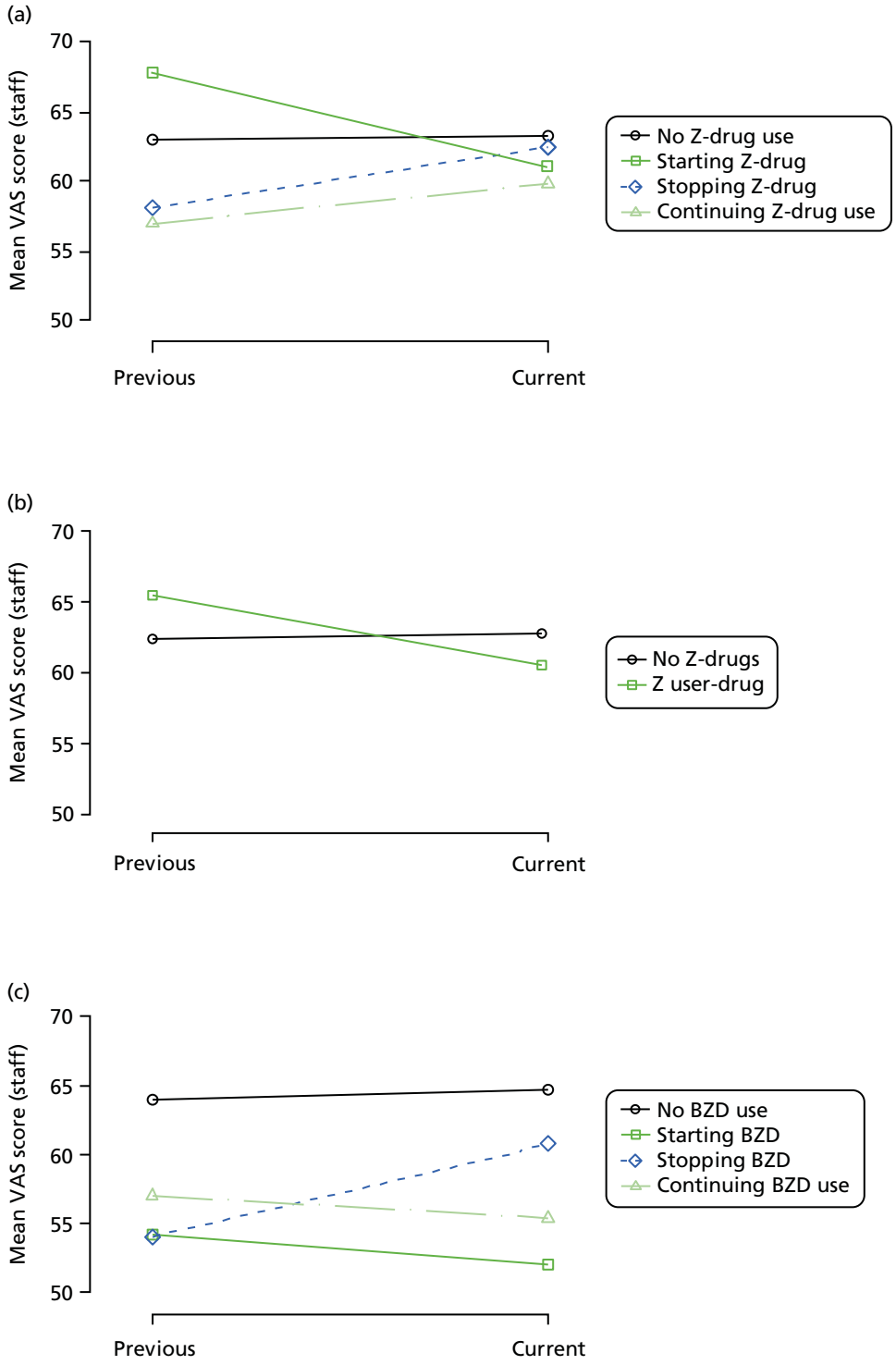

FIGURE 9 Association between changing hypnotic use status between previous and current visit on VAS scores (higher scores represent better QoL) at previous and current visit (a, c and e). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (b, d and f). Data from the REDIC-NH study. AP, antipsychotic. (*continued*)

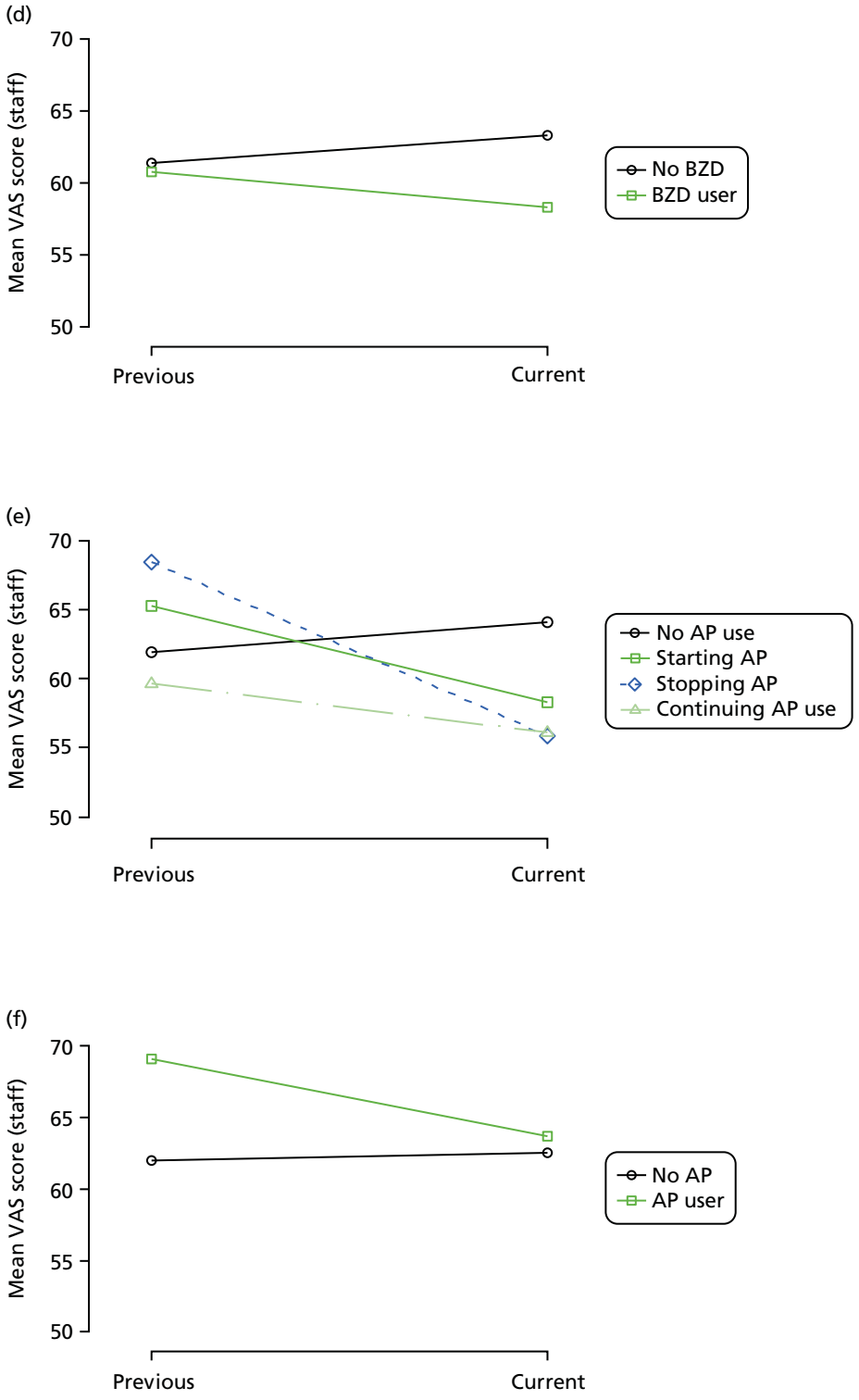

FIGURE 9 Association between changing hypnotic use status between previous and current visit on VAS scores (higher scores represent better QoL) at previous and current visit (a, c and e). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (b, d and f). Data from the REDIC-NH study. AP, antipsychotic.

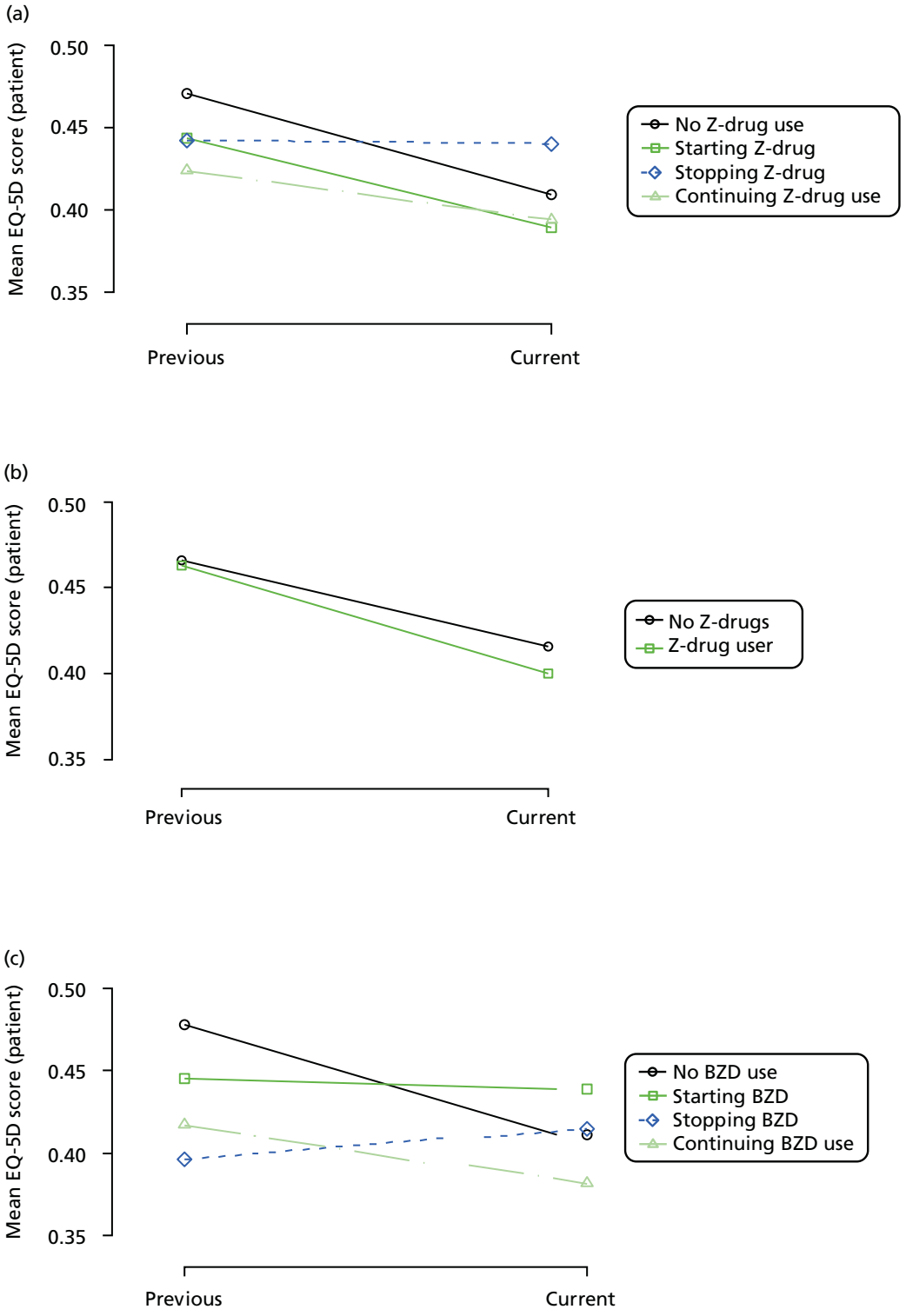

FIGURE 10 Association between changing hypnotic use status between previous and current visit on EQ-5D scores (higher scores represent better QoL) at previous and current visit (a, c and e). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (b, d and f). Data from the REDIC-NH study. AP, antipsychotic. (*continued*)

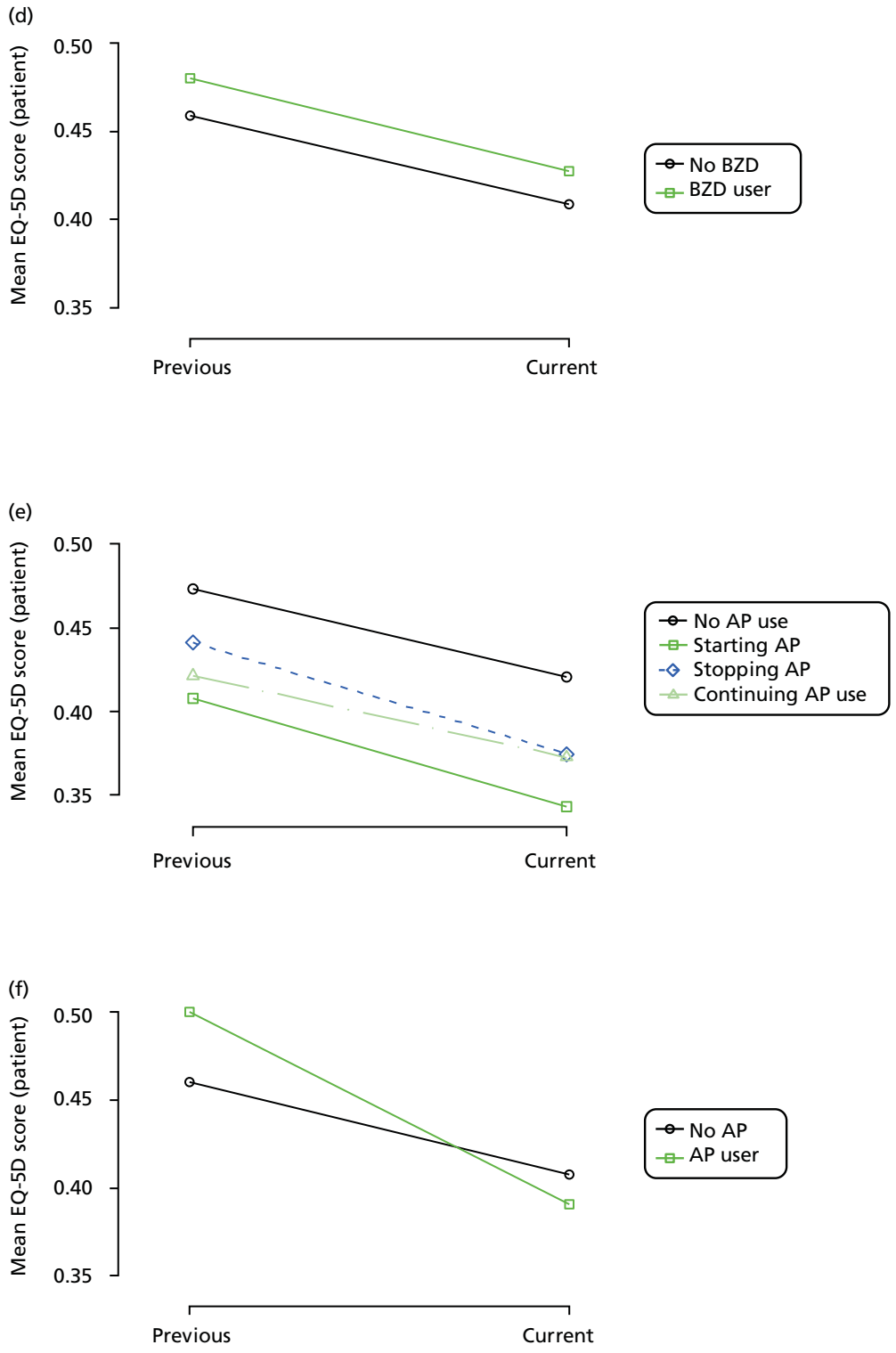

FIGURE 10 Association between changing hypnotic use status between previous and current visit on EQ-5D scores (higher scores represent better QoL) at previous and current visit (a, c and e). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (b, d and f). Data from the REDIC-NH study. AP, antipsychotic.

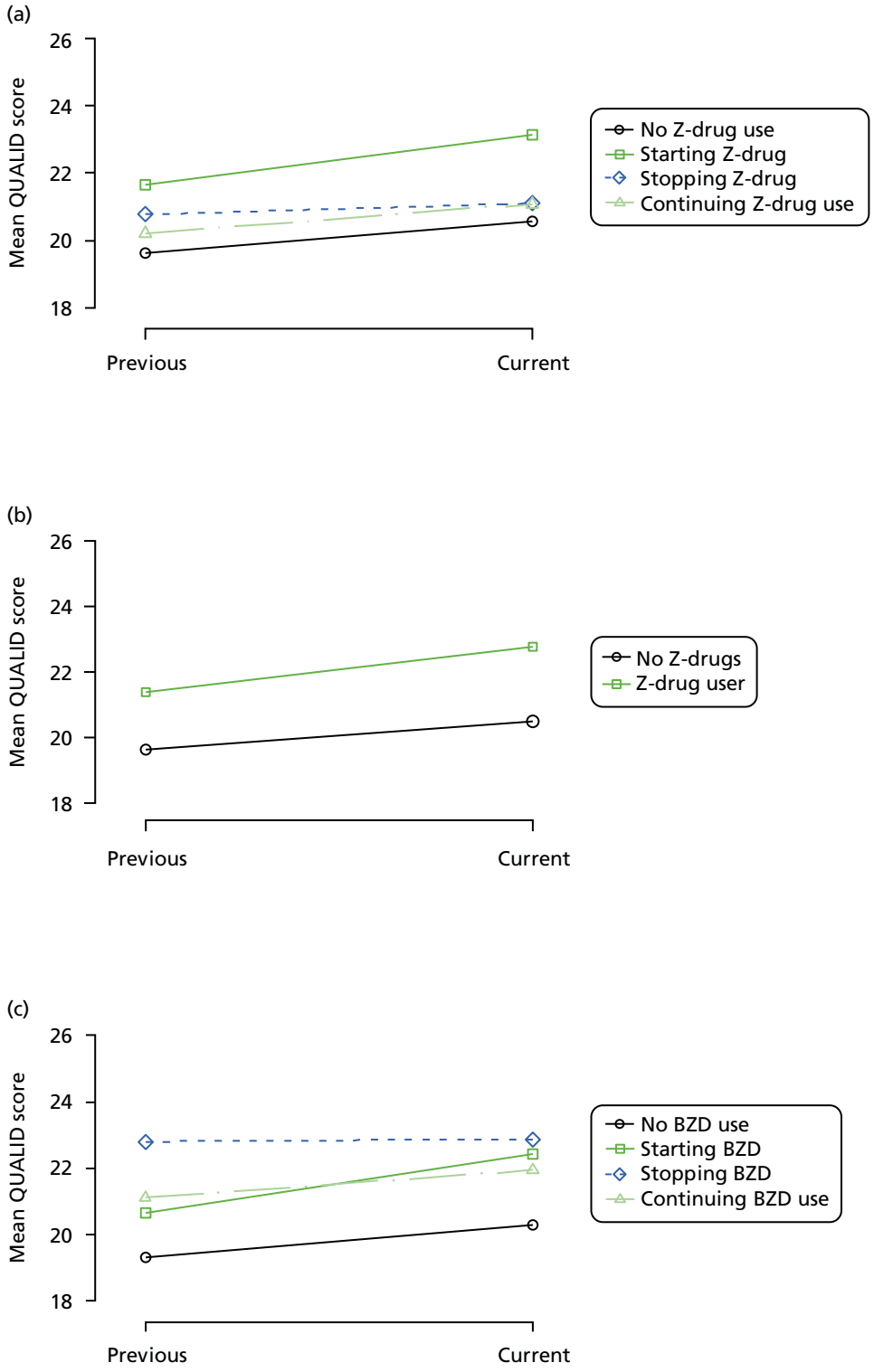

FIGURE 11 Association between changing hypnotic use status between previous and current visit on QUALID scores (higher scores represent lower QoL) at previous and current visit (a, c and e). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (b, d and f). Data from the REDIC-NH study. AP, antipsychotic. (*continued*)

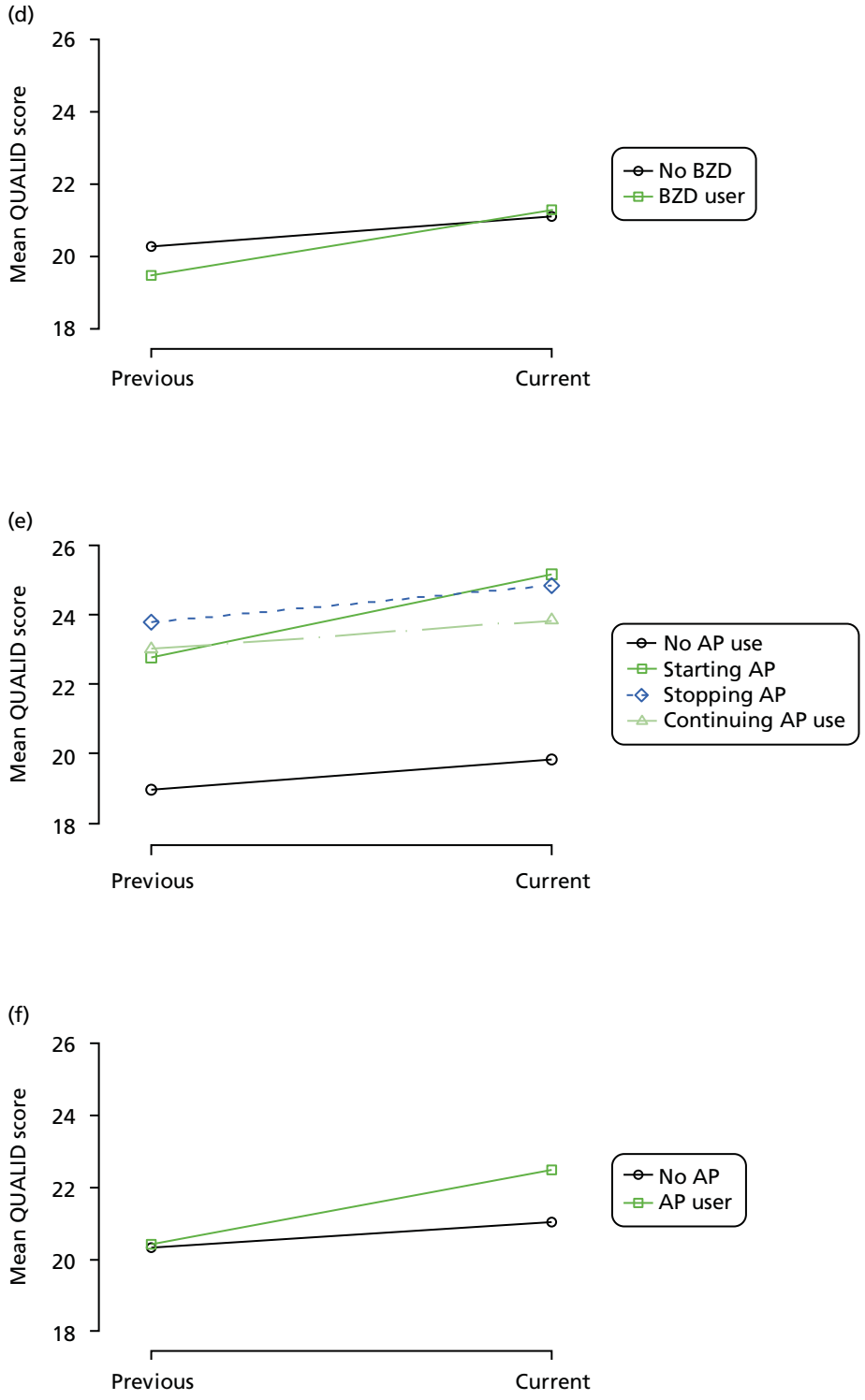

FIGURE 11 Association between changing hypnotic use status between previous and current visit on QUALID scores (higher scores represent lower QoL) at previous and current visit (a, c and e). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (b, d and f). Data from the REDIC-NH study. AP, antipsychotic.

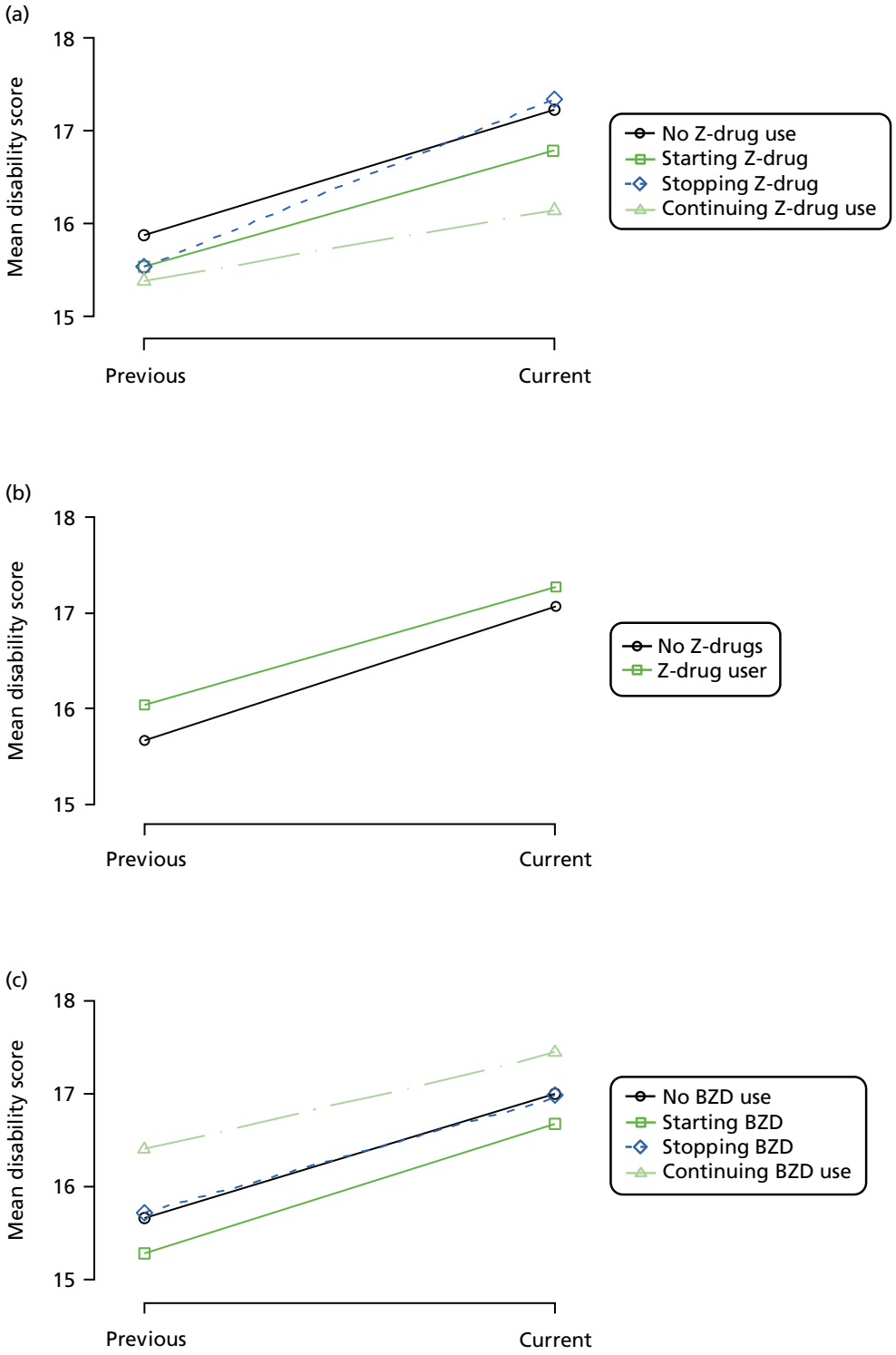

FIGURE 12 Association between changing hypnotic use status between previous and current visit on disability scores (higher scores represent more disability) at previous and current visit (a, c and e). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (b, d and f). Data from the REDIC-NH study. AP, antipsychotic. (*continued*)

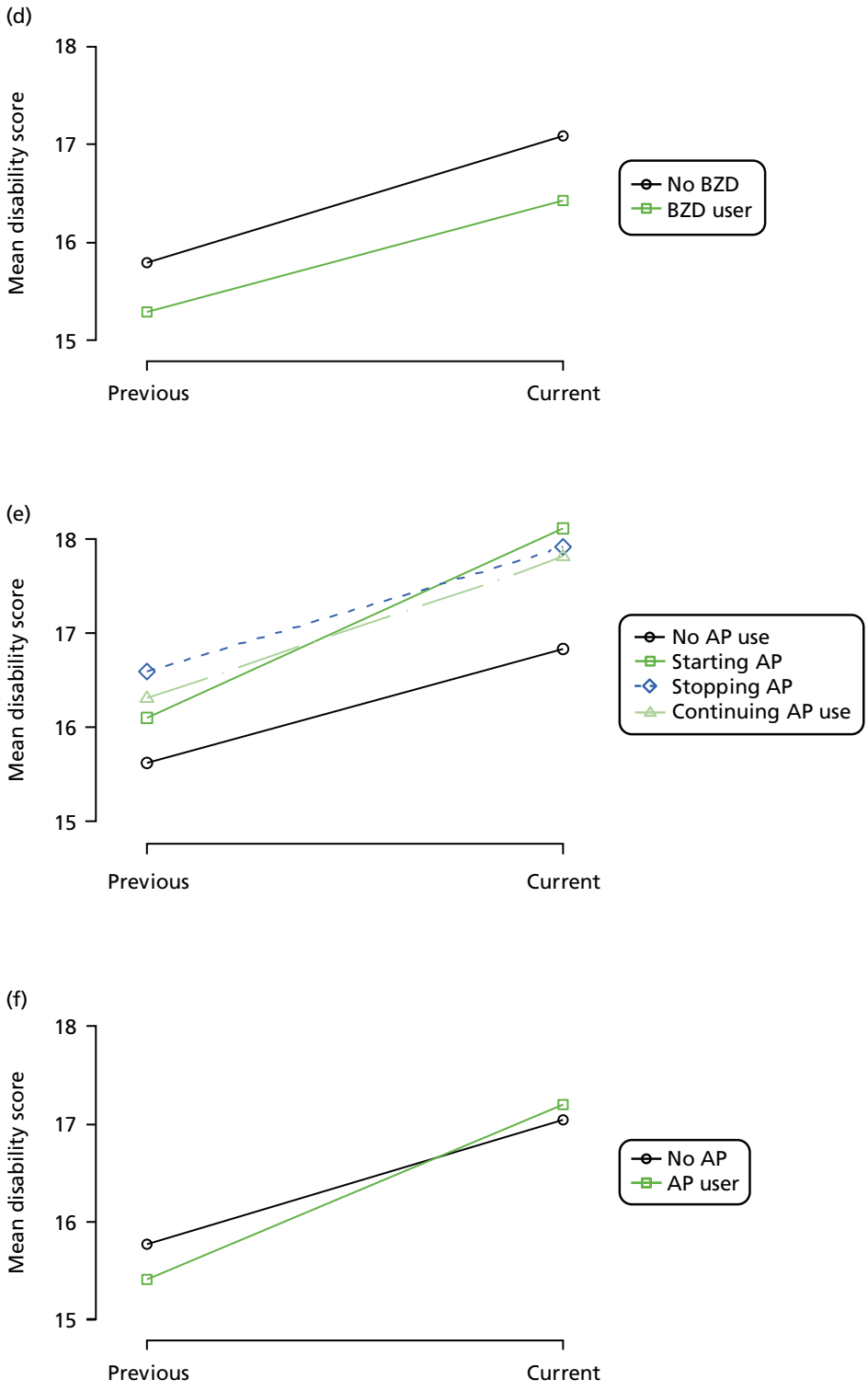

FIGURE 12 Association between changing hypnotic use status between previous and current visit on disability scores (higher scores represent more disability) at previous and current visit (a, c and e). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (b, d and f). Data from the REDIC-NH study. AP, antipsychotic.

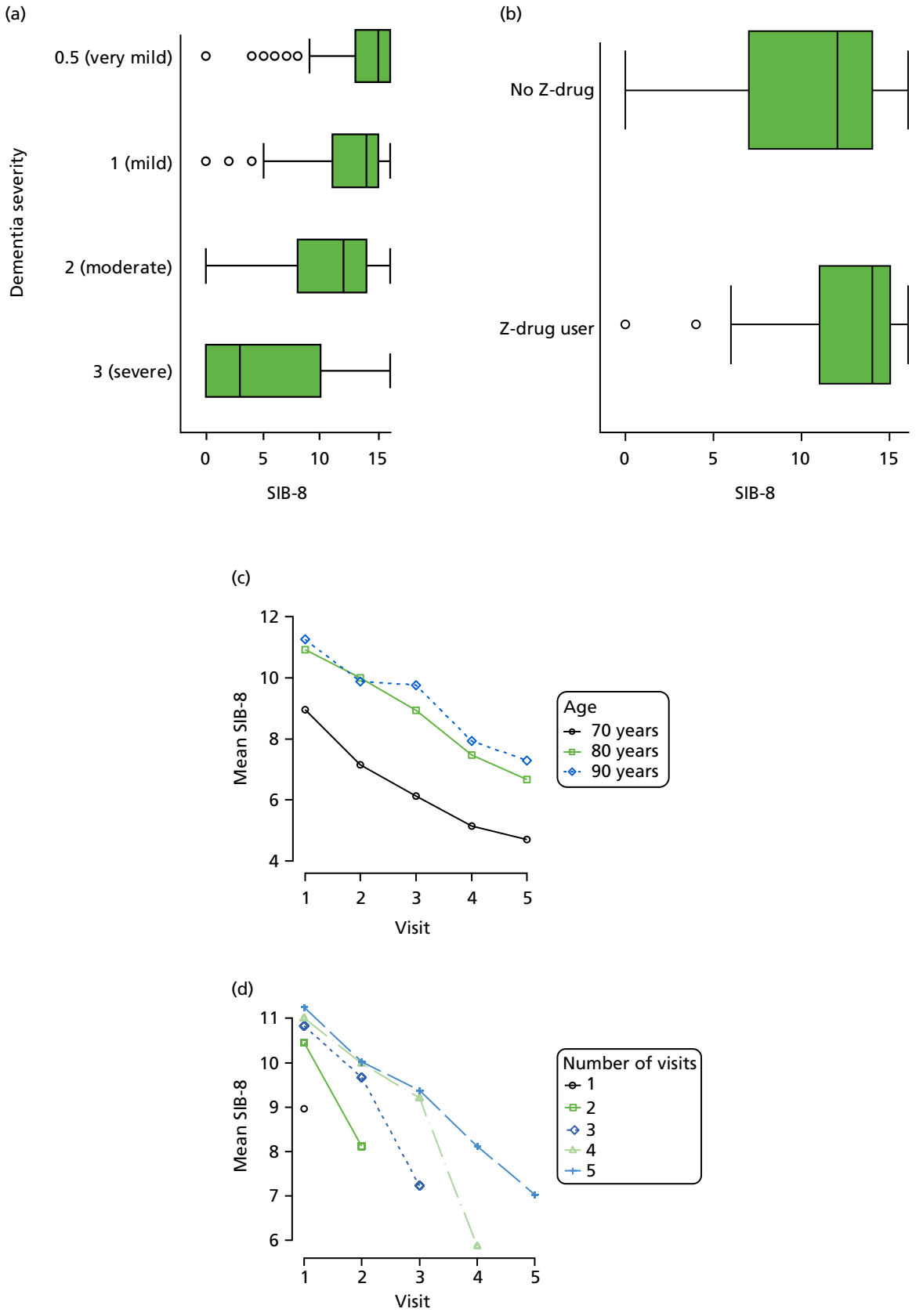

FIGURE 13 (a) Distribution of SIB-8 with respect to dementia severity; (b) distribution of SIB-8 with respect to Z-drug use; (c) mean score over REDIC visit, stratified by age group; and (d) mean score over REDIC visit, stratified by number of visits completed.

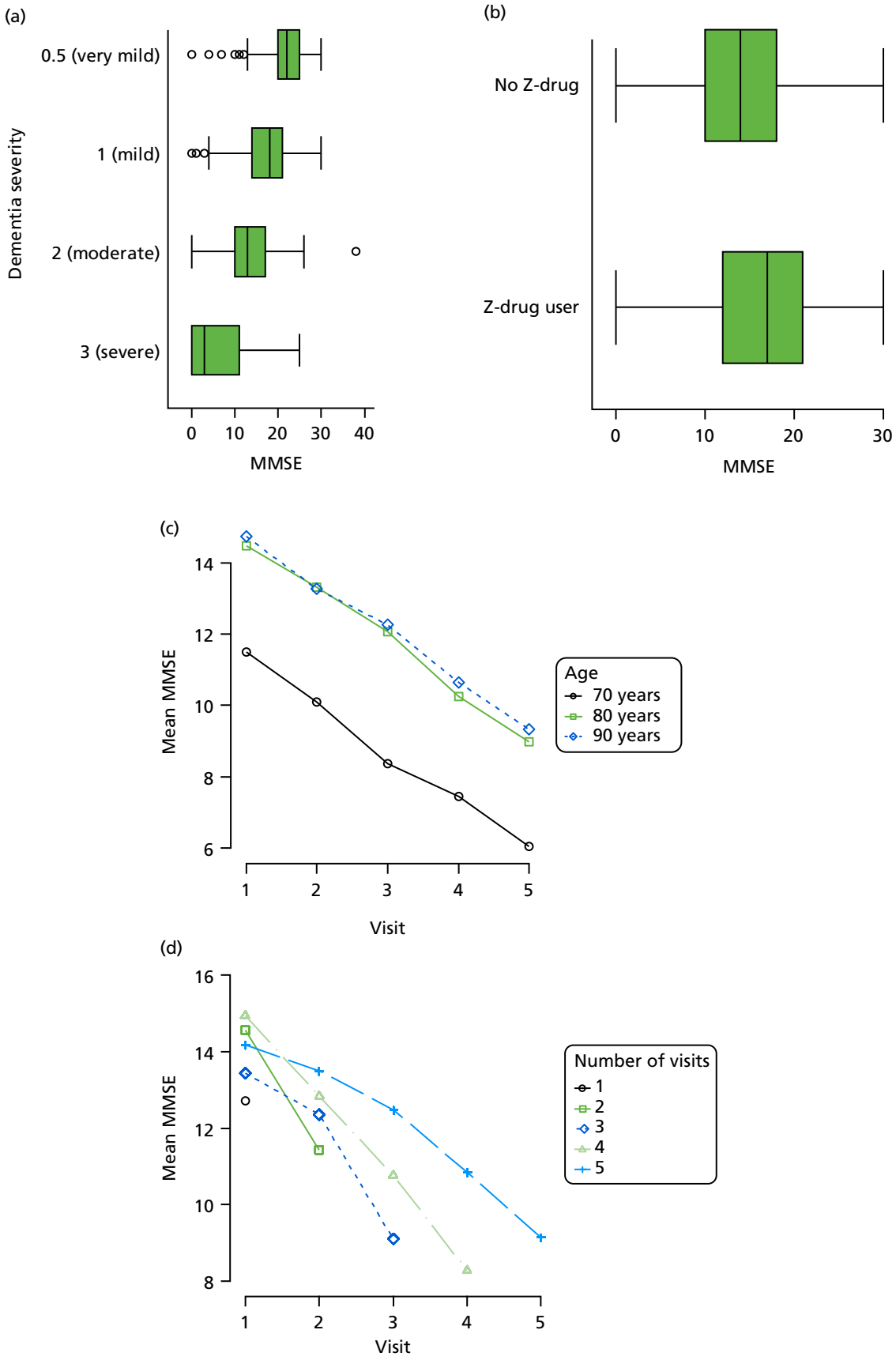

FIGURE 14 (a) Distribution of MMSE with respect to dementia severity; (b) distribution of MMSE with respect to Z-drug use; (c) mean score over REDIC visit, stratified by age group; and (d) mean score over REDIC visit, stratified by number of visits completed.

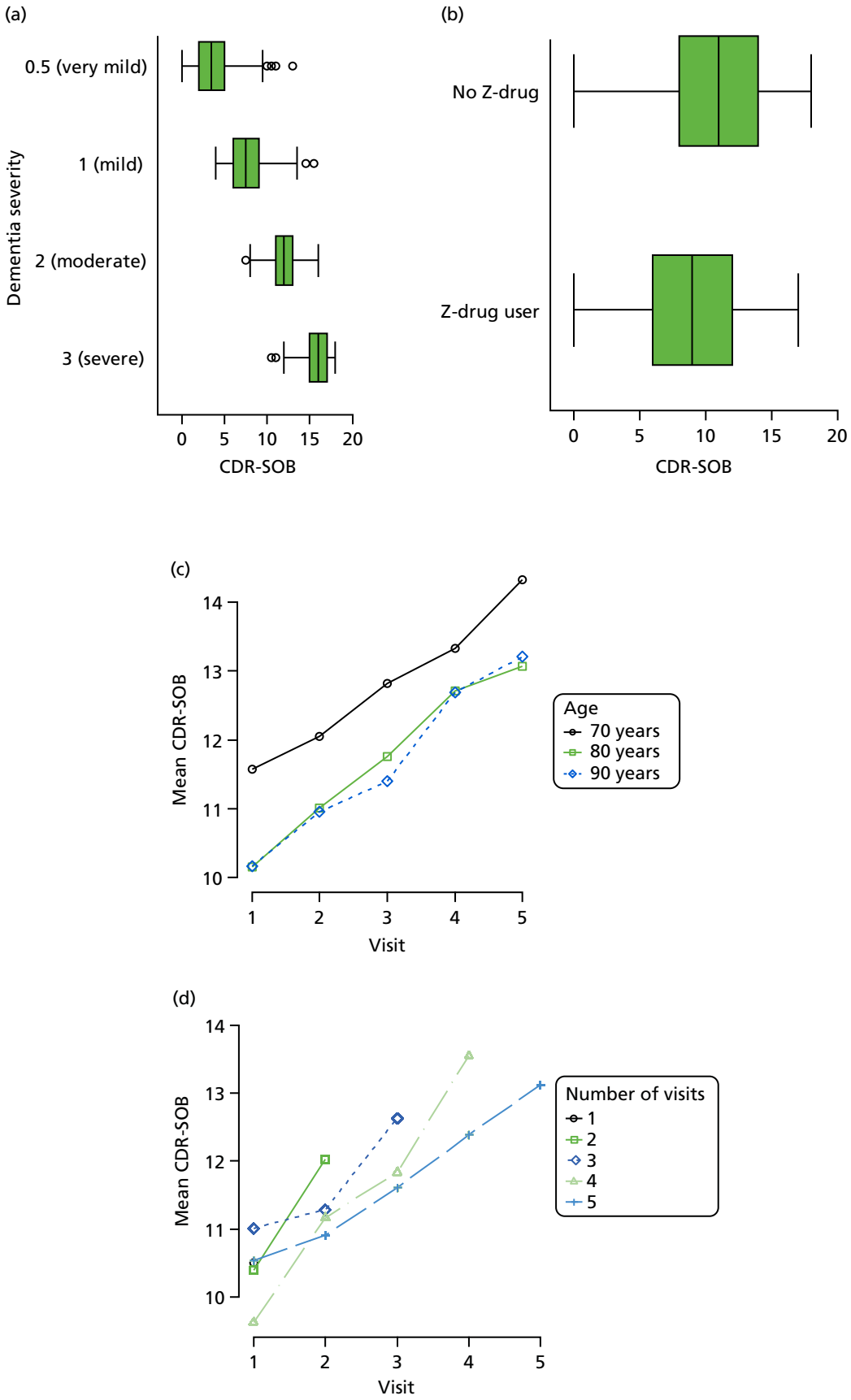

FIGURE 15 (a) Distribution of CDR-SOB with respect to dementia severity; (b) distribution of CDR-SOB with respect to dementia and Z-drug; (c) mean score over REDIC visit, stratified by age group; and (d) mean score over REDIC visit, stratified number of visits completed.

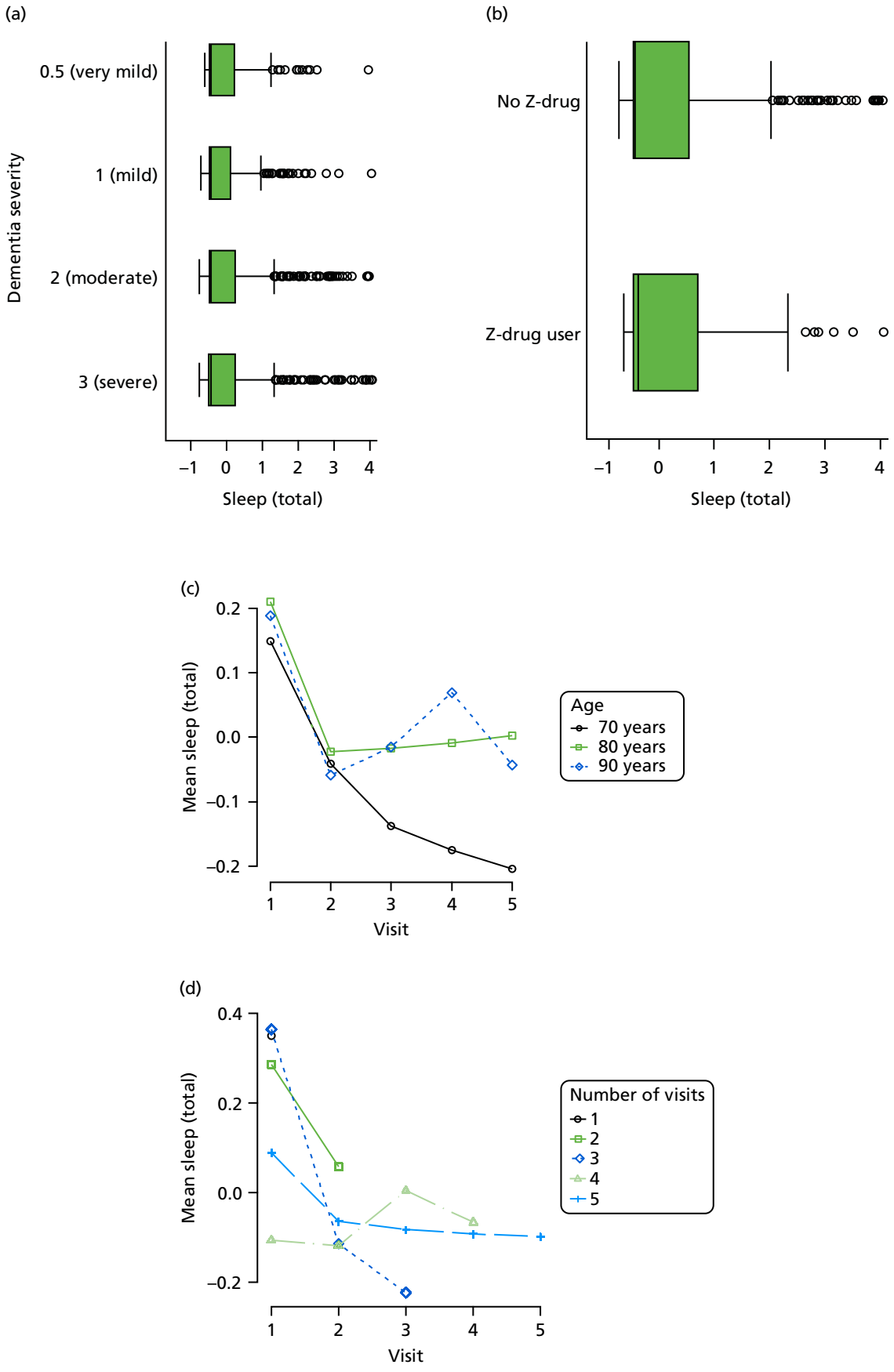

FIGURE 16 (a) Distribution of sleep disturbance with respect to dementia severity; (b) distribution of sleep disturbance with respect to Z-drug use; (c) mean score over REDIC visit, stratified by age group; and (d) mean score over REDIC visit, stratified by number of visits completed.

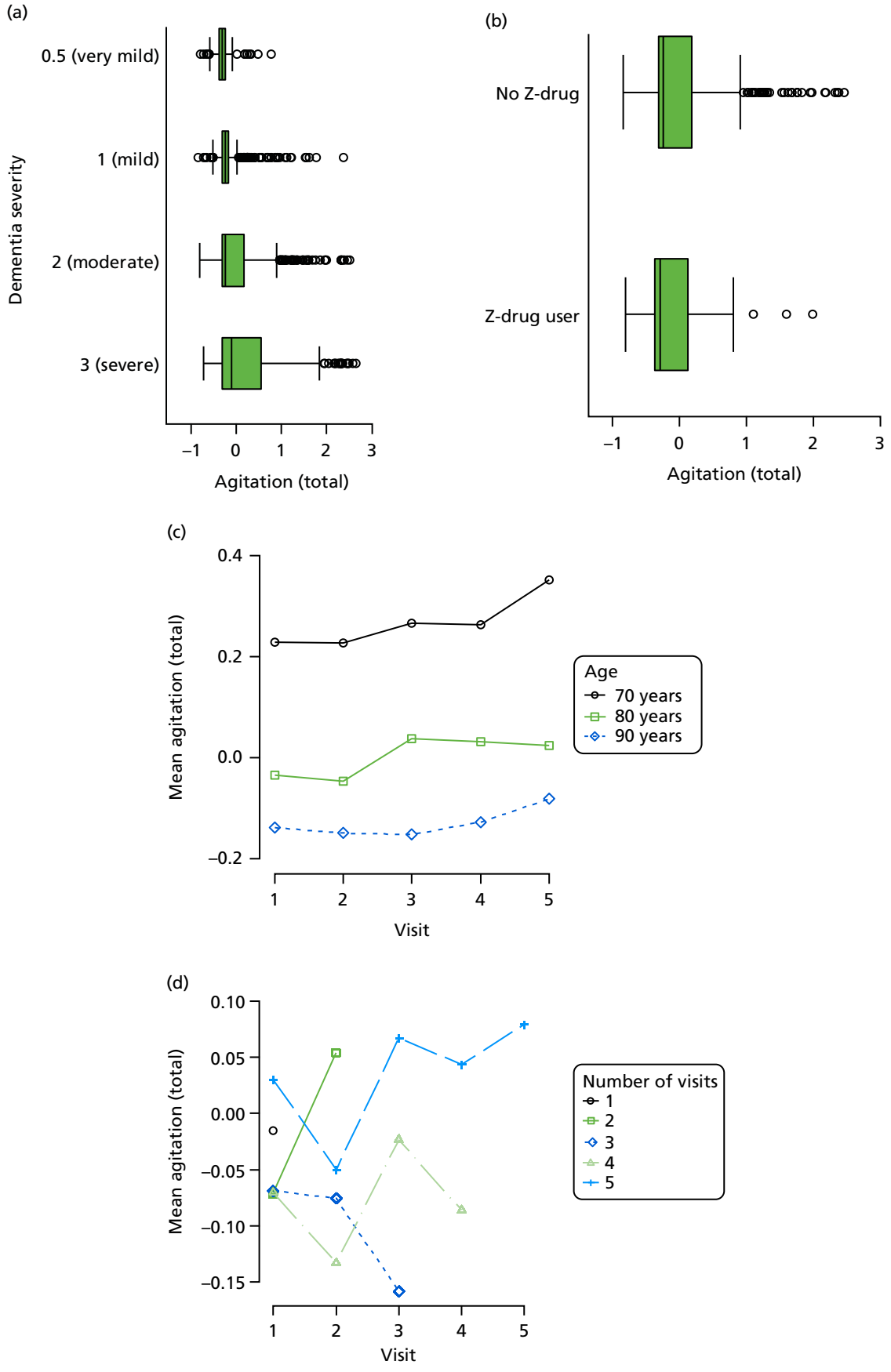

FIGURE 17 (a) Distribution of agitation with respect to dementia severity; (b) distribution of agitation with respect to Z-drug use; (c) mean score over REDIC visit, stratified by age group; and (d) mean score over REDIC visit, stratified by number of visits completed.

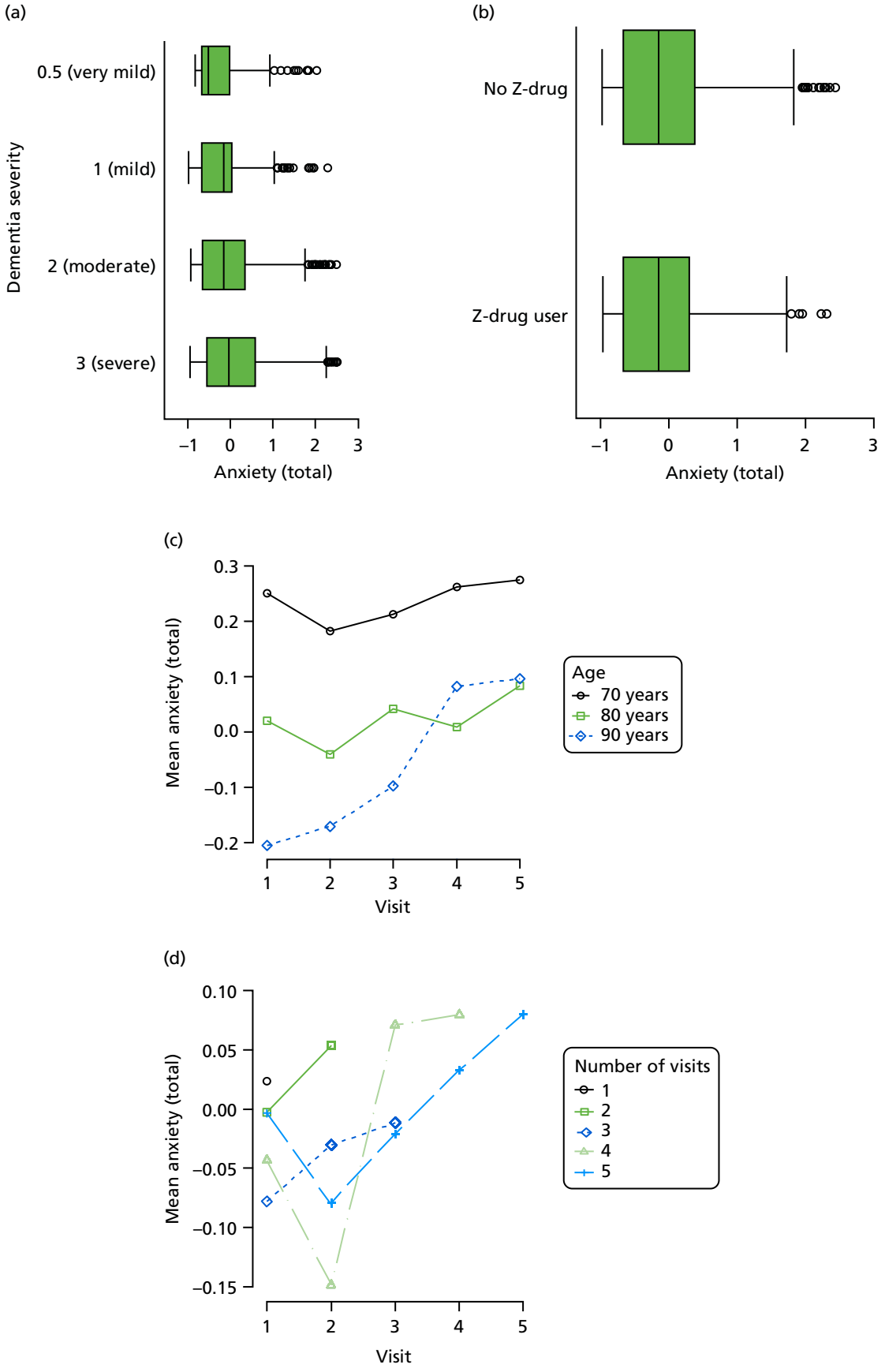

FIGURE 18 (a) Distribution of anxiety with respect to dementia severity; (b) distribution of anxiety with respect to Z-drug use; (c) mean score over REDIC visit, stratified by age group; and (d) mean score over REDIC visit, stratified by number of visits completed.

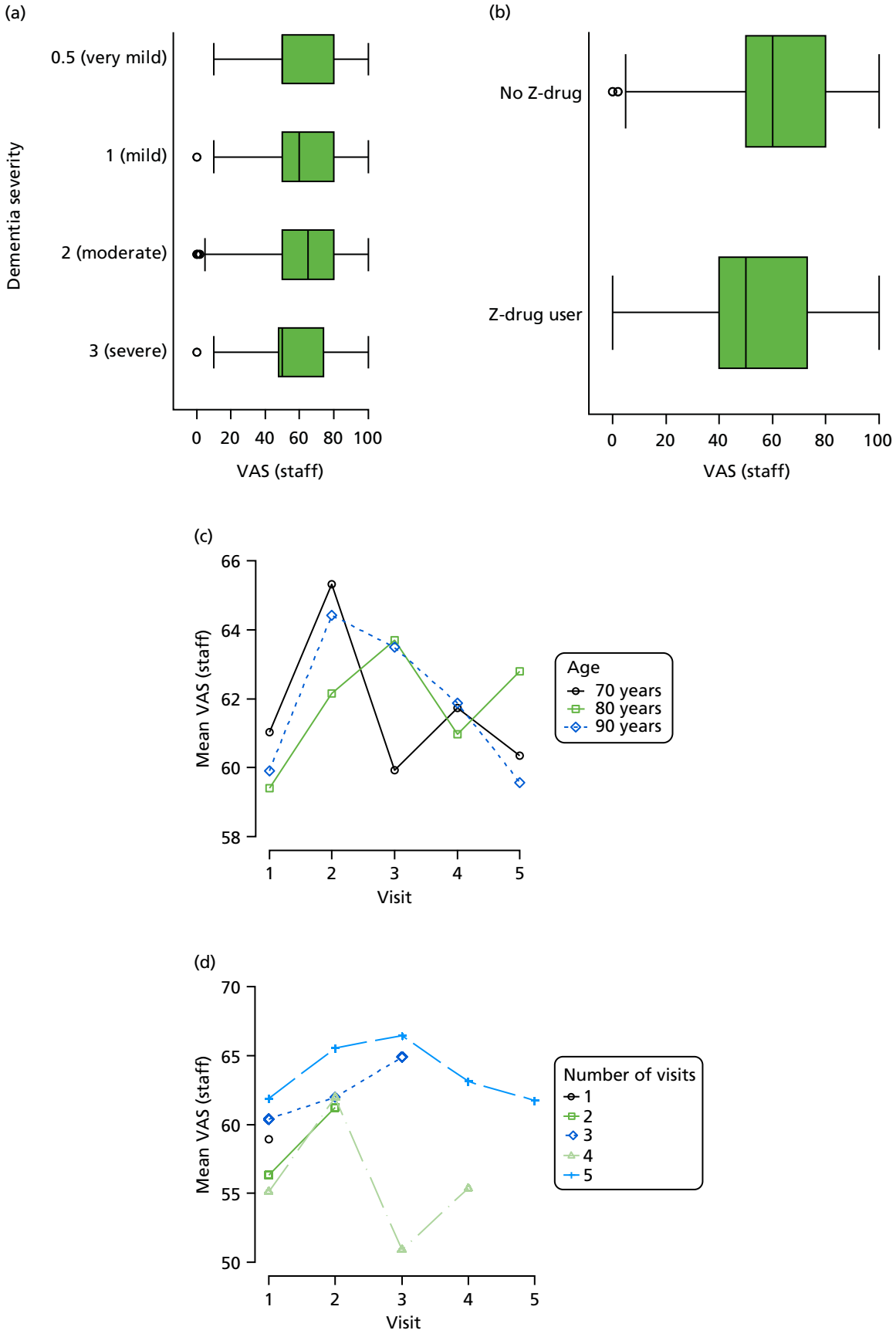

FIGURE 19 (a) Distribution of VAS with respect to dementia severity; (b) distribution of VAS with respect to Z-drug use; (c) mean score over REDIC visit, stratified by age group; and (d) mean score over REDIC visit, stratified by number of visits completed.

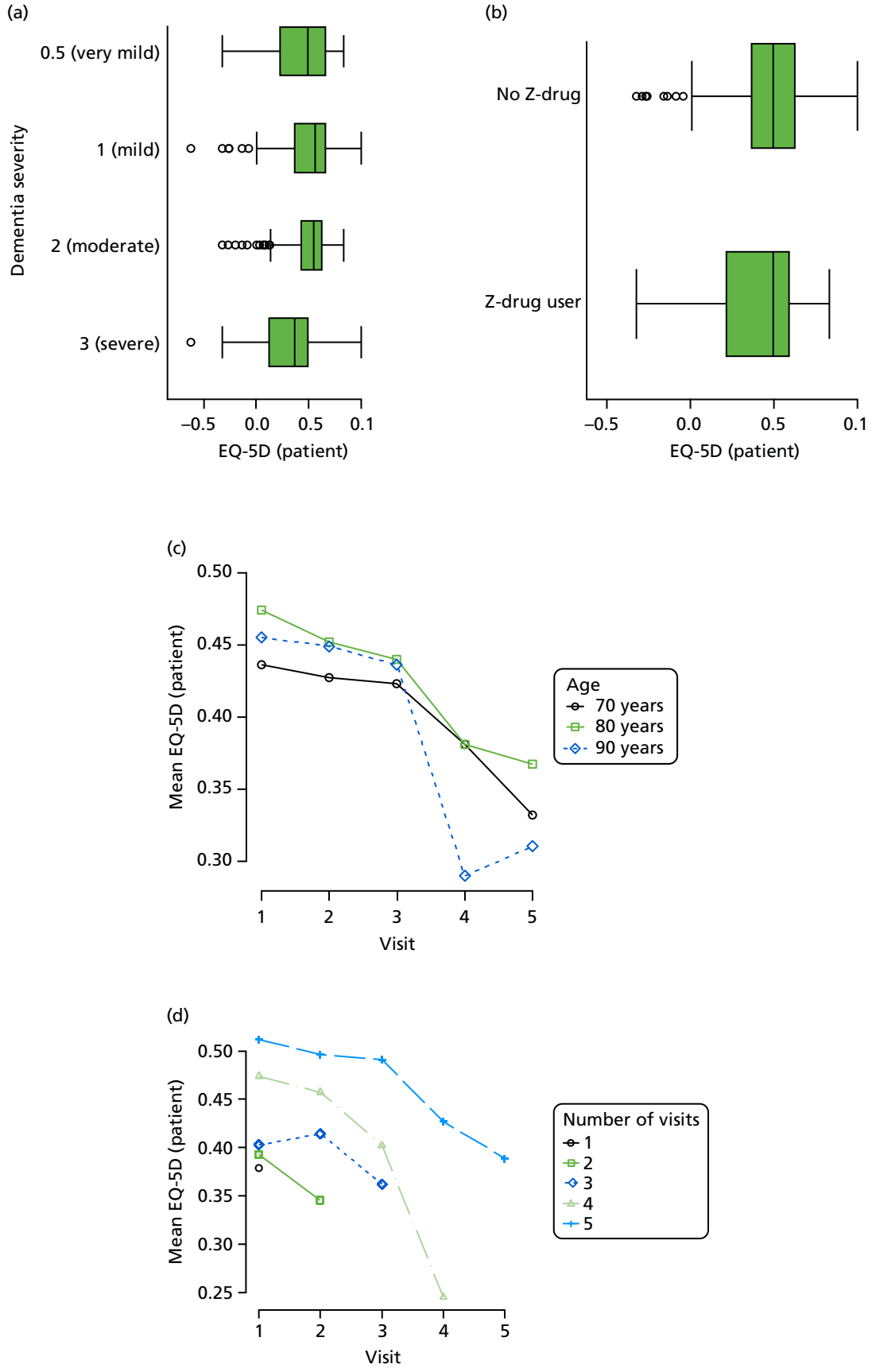

FIGURE 20 (a) Distribution of EQ-5D with respect to dementia severity; (b) distribution of EQ-5D with respect to Z-drug; (c) mean score over REDIC visit, stratified by age group; and (d) mean score over REDIC visit, stratified by number of visits completed.

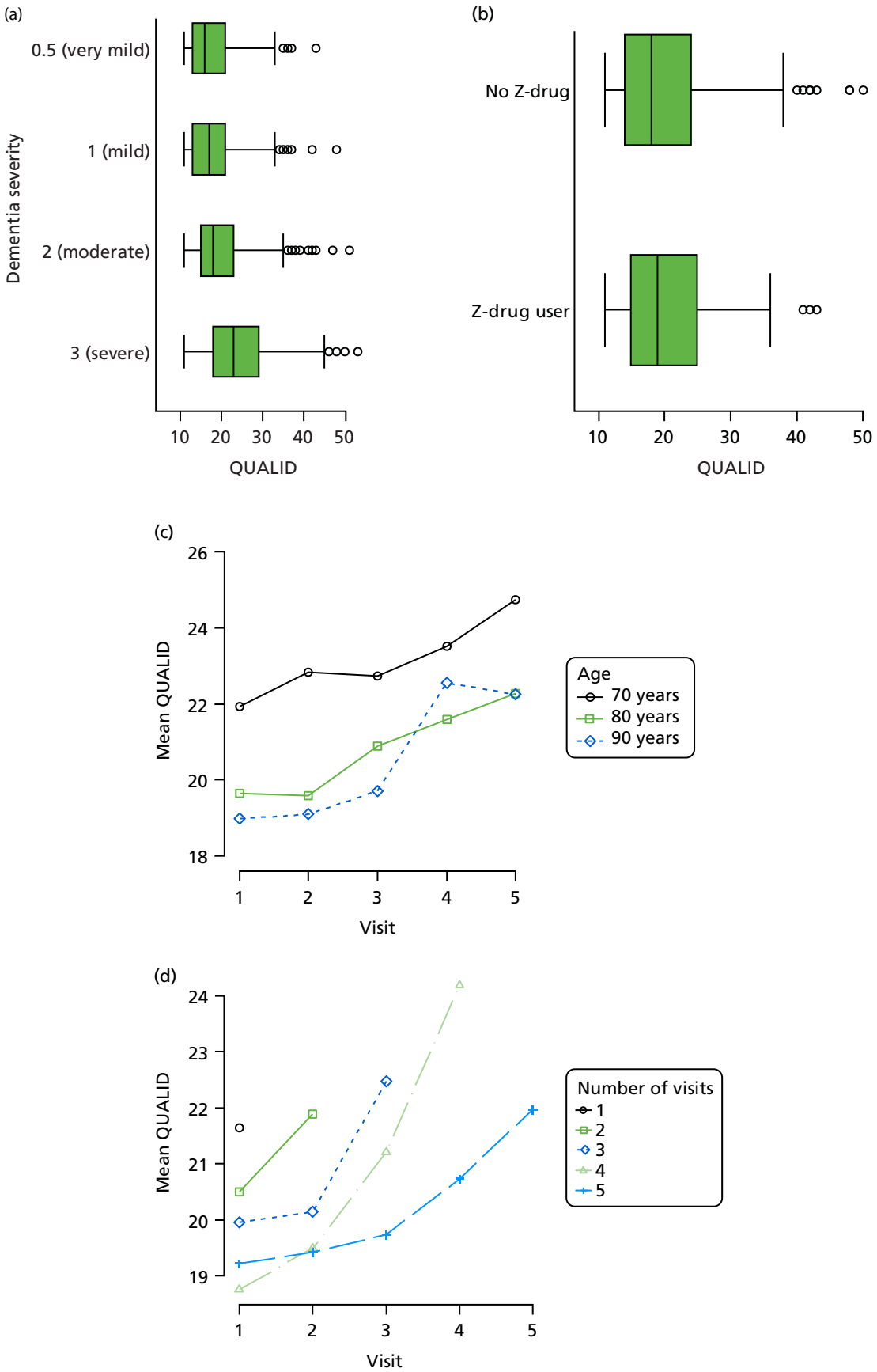

FIGURE 21 (a) Distribution of QUALID with respect to dementia severity; (b) distribution of QUALID with respect to Z-drug use; (c) mean score over REDIC visit, stratified by age group; and (d) mean score over REDIC visit, stratified by number of visits completed.

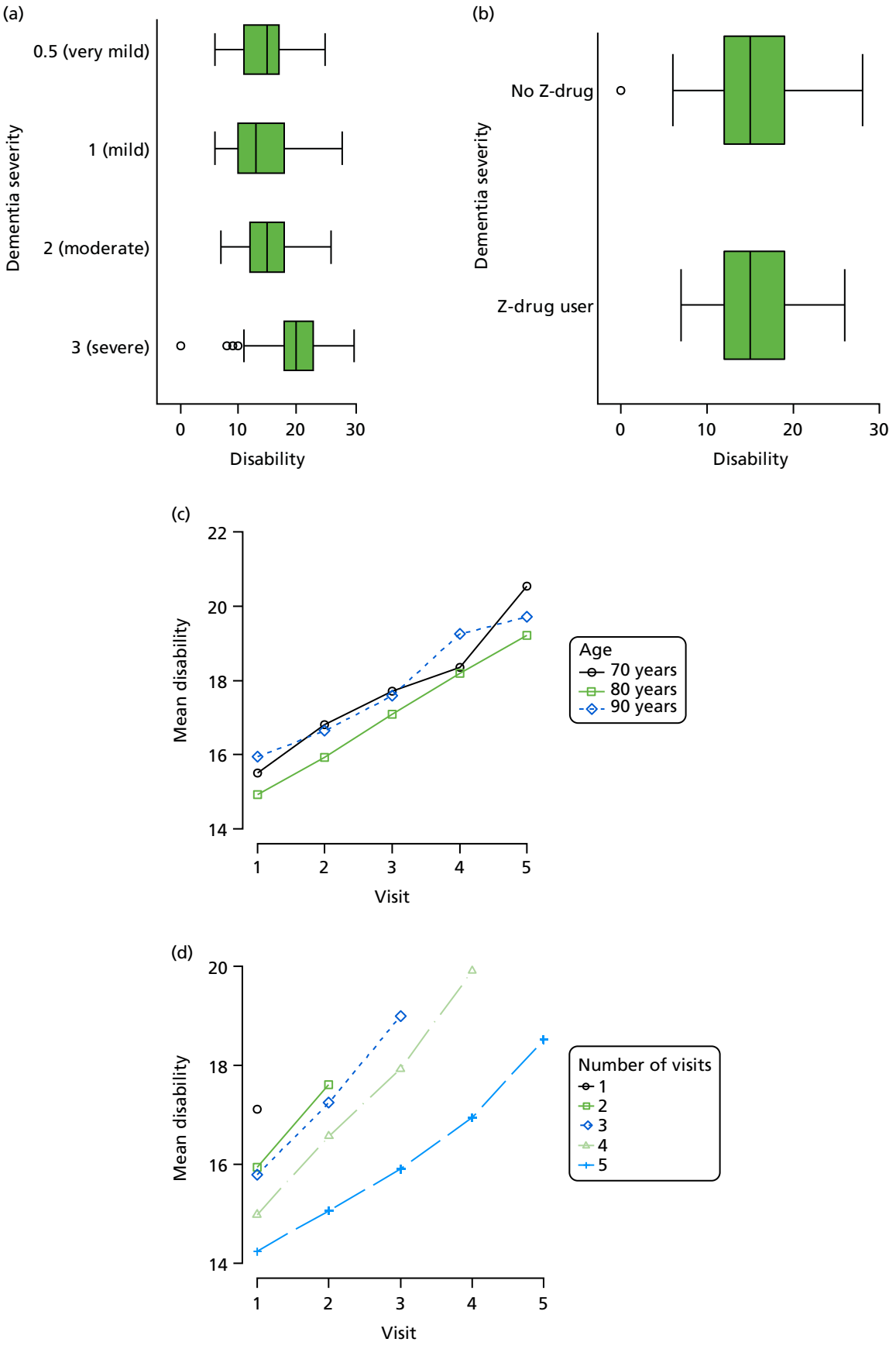

FIGURE 22 (a) Distribution of disability (Lawton Physical Self-Maintenance Scale) with respect to dementia severity; (b) distribution of disability (Lawton Physical Self-Maintenance Scale) with respect to Z-drug use; (c) mean score over REDIC visit, stratified by age group; and (d) mean score over REDIC visit, stratified by number of visits completed.

Appendix 4 Additional NACC study analyses

TABLE 48 The number of participants who underwent each visit and provided medication data as a percentage of the initial cohort, and the proportion of visits at which Z-drugs, BZDs, antipsychotics and antidepressants were reported at each

Visit number	Visits, *n* (%)	Z-drugs, *n* (%)	BZDs, *n* (%)	Antipsychotics, *n* (%)	Antidepressants, *n* (%)
1	16,862 (100)	373 (2)	1276 (8)	1454 (9)	6742 (40)
2	9890 (59)	198 (2)	776 (8)	1070 (11)	4397 (44)
3	6375 (38)	121 (2)	557 (9)	845 (13)	3011 (47)
4	4020 (24)	75 (2)	371 (9)	637 (16)	1980 (49)
5	2441 (14)	42 (2)	265 (11)	420 (17)	1212 (50)
6	1469 (9)	26 (2)	164 (11)	275 (19)	741 (50)
7	838 (5)	12 (1)	86 (10)	167 (20)	388 (46)
8	437 (3)	8 (2)	39 (9)	87 (20)	206 (47)
9	238 (1)	2 (1)	23 (10)	50 (21)	116 (49)
10	111 (1)	1 (1)	15 (14)	28 (25)	51 (46)
11	51 (0.3)	1 (2)	8 (16)	11 (22)	26 (51)
12	19 (0.1)	0 (0)	5 (26)	6 (32)	13 (68)

TABLE 49 The number of participants continuing, stopping or starting Z-drugs, BZDs or antipsychotics between NACC visits

	No use at previous wave			Use at previous wave		
	Total, *N* (%)	No use, *n* (%)	Starting, *n* (%)	Total, *N* (%)	Stopping, *n* (%)	Continued, *n* (%)
Z-drugs	25,289 (100)	25,070 (99)	219 (1)	522 (100)	257 (49)	265 (51)
BZDs	23,851 (100)	22,898 (96)	953 (4)	1960 (100)	615 (31)	1345 (69)
Antipsychotics	23,102 (100)	21,658 (94)	1444 (6)	2709 (100)	572 (21)	2137 (79)

TABLE 50 The ORs showing the predictors of continuing use of hypnotics among those using each drug at the prior wave

Factor	Level	Continuing Z-drugs, OR (95% CI)	Continuing BZDs, OR (95% CI)	Continuing antipsychotics, OR (95% CI)
Drug use	Z-drug use		0.72 (0.43 to 1.22)	0.73 (0.38 to 1.08)
	BZD use	0.93 (0.53 to 1.64)		1.01 (0.75 to 1.27)
	AP use	1.26 (0.72 to 2.21)	1.48** (1.13 to 1.94)	
Education	Per year	0.96 (0.92 to 1.00)	0.99 (0.96 to 1.02)	0.99 (0.96 to 1.02)
Sex	Female	1.00 (0.65 to 1.52)	0.86 (0.68 to 1.08)	0.81* (0.63 to 0.98)
CDR	Minimal	1 (Ref)	1 (Ref)	1 (Ref)
	Mild	1.41 (0.88 to 2.25)	0.92 (0.70 to 1.22)	1.30 (0.76 to 1.84)
	Moderate	0.72 (0.39 to 1.34)	0.73 (0.53 to 1.02)	1.44 (0.83 to 2.05)
	Severe	0.87 (0.46 to 1.67)	0.63** (0.45 to 0.88)	1.08 (0.64 to 1.52)
Age (years)	< 61	1 (Ref)	1 (Ref)	1 (Ref)
	61–70	0.81 (0.43 to 1.52)	0.70* (0.50 to 0.99)	1.05 (0.71 to 1.38)
	71–80	0.80 (0.43 to 1.46)	0.55*** (0.40 to 0.77)	0.98 (0.68 to 1.29)
	81–90	0.70 (0.36 to 1.36)	0.60** (0.41 to 0.88)	0.93 (0.61 to 1.25)
	≥ 90	0.87 (0.27 to 2.78)	0.62 (0.25 to 1.52)	1.29 (–0.005 to 2.58)
Sleep	None	1 (Ref)	1 (Ref)	1 (Ref)
	Mild	0.97 (0.60 to 1.57)	0.78 (0.58 to 1.04)	1.21 (0.87 to 1.55)
	Moderate	0.85 (0.49 to 1.47)	1.15 (0.85 to 1.57)	1.04 (0.75 to 1.34)
	Severe	0.58 (0.28 to 1.22)	1.11 (0.72 to 1.73)	1.00 (0.61 to 1.39)
Anxiety	None	1 (Ref)	1 (Ref)	1 (Ref)
	Mild	1.23 (0.77 to 1.98)	0.98 (0.77 to 1.26)	1.06 (0.78 to 1.33)
	Moderate	0.93 (0.54 to 1.62)	0.86 (0.65 to 1.14)	0.85 (0.61 to 1.09)
	Severe	1.59 (0.55 to 4.59)	0.92 (0.60 to 1.40)	0.95 (0.56 to 1.35)
Agitation	None	1 (Ref)	1 (Ref)	1 (Ref)
	Mild	0.76 (0.47 to 1.21)	1.20 (0.93 to 1.56)	1.07 (0.81 to 1.32)
	Moderate	0.76 (0.42 to 1.37)	1.03 (0.76 to 1.40)	1.50** (1.07 to 1.93)
	Severe	0.92 (0.35 to 2.39)	1.18 (0.77 to 1.81)	1.30 (0.78 to 1.81)

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
AP, antipsychotic; Ref, reference.

TABLE 51 The associations between hypnotic use and outcomes as estimated by a marginal structural model

	β (95% CI)		
Outcome measure	Z-drug	BZD	Antipsychotic
CDR-SOB	0.21 (–0.25 to 0.67)	1.37*** (1.10 to 1.65)	1.98*** (1.73 to 2.23)
MMSE	0.17 (–0.40 to 0.75)	–1.26*** (–1.76 to –0.77)	–1.81*** (–2.27 to –1.36)
Animal fluency	0.25 (–0.42 to 0.92)	–0.47* (–0.88 to –0.06)	–0.92*** (–1.30 to –0.53)
Delta trail time	–5.14 (–23.14 to 12.85)	–0.87 (–11.34 to 9.60)	1.85 (–8.61 to 12.30)
Sleep	0.23** (0.08 to 0.38)	0.11** (0.03 to 0.18)	0.18*** (0.11 to 0.24)
Agitation	0.14* (0.00 to 0.28)	0.19*** (0.12 to 0.27)	0.35*** (0.28 to 0.42)
Anxiety	0.05 (–0.08 to 0.18)	0.24*** (0.16 to 0.31)	0.18*** (0.12 to 0.25)
NPI (excluding sleep)	0.13 (–0.56 to 0.82)	1.16*** (0.81 to 1.51)	1.62*** (1.29 to 1.95)
GDS	–0.29 (–0.72 to 0.13)	0.00 (–0.25 to 0.26)	0.18 (–0.05 to 0.41)
Disability	–0.19 (–0.93 to 0.56)	1.27*** (0.81 to 1.72)	2.25*** (1.77 to 2.72)

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

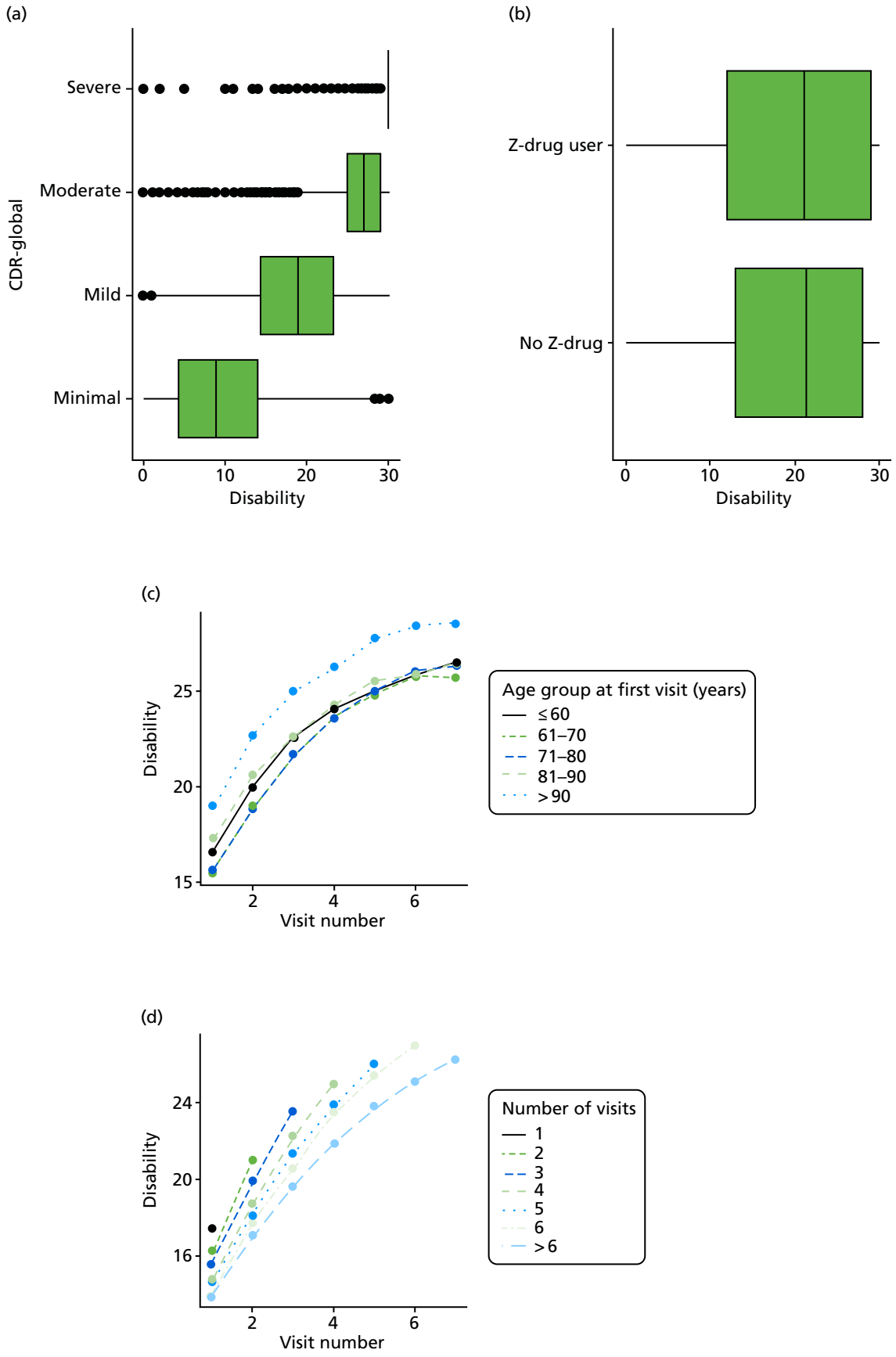

FIGURE 23 (a) Distribution of disability with respect to dementia severity; (b) distribution of disability with respect to Z-drug use; (c) mean score over NACC visit, stratified by age group; and (d) mean score over NACC visit, stratified by number of visits completed.

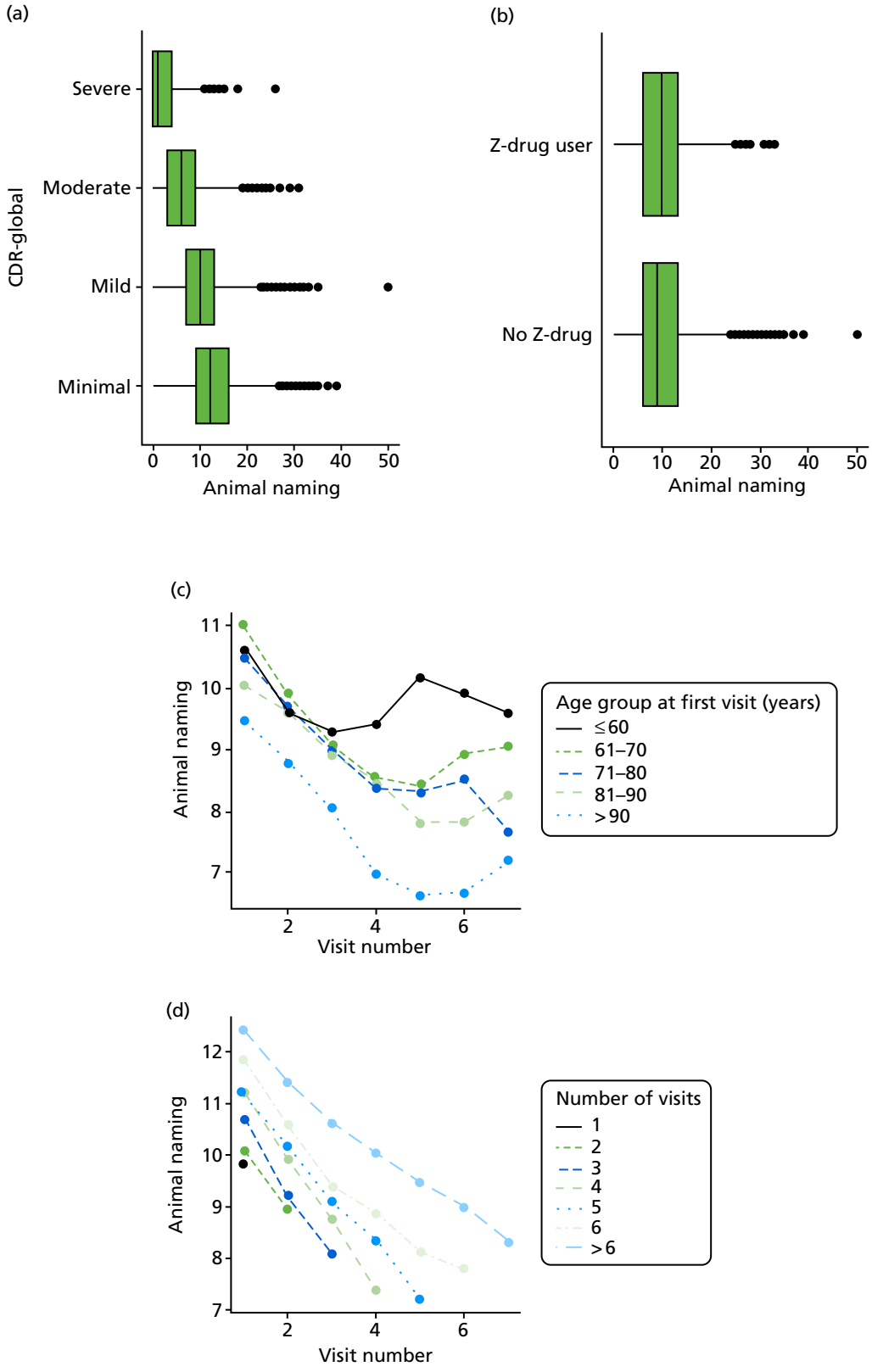

FIGURE 24 (a) Distribution of animal fluency with respect to dementia severity; (b) distribution of animal fluency with respect to Z-drug use; (c) mean score over NACC visit, stratified by age group; and (d) mean score over NACC visit, stratified by number of visits completed.

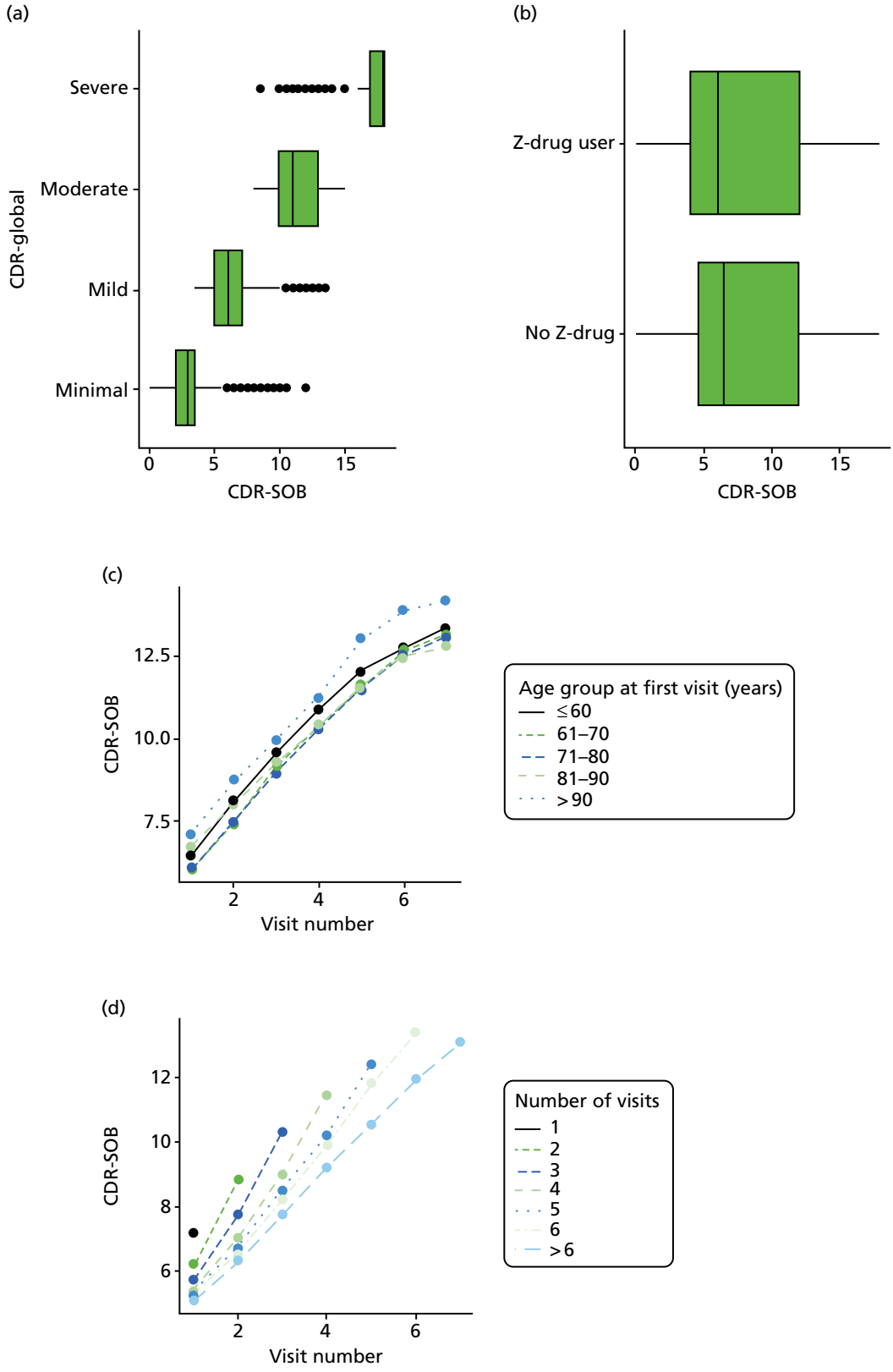

FIGURE 25 (a) Distribution of CDR-SOB with respect to dementia severity; (b) distribution of CDR-SOB with respect to Z-drug use; (c) mean score over NACC visit, stratified by age group; and (d) mean score over NACC visit, stratified by number of visits completed.

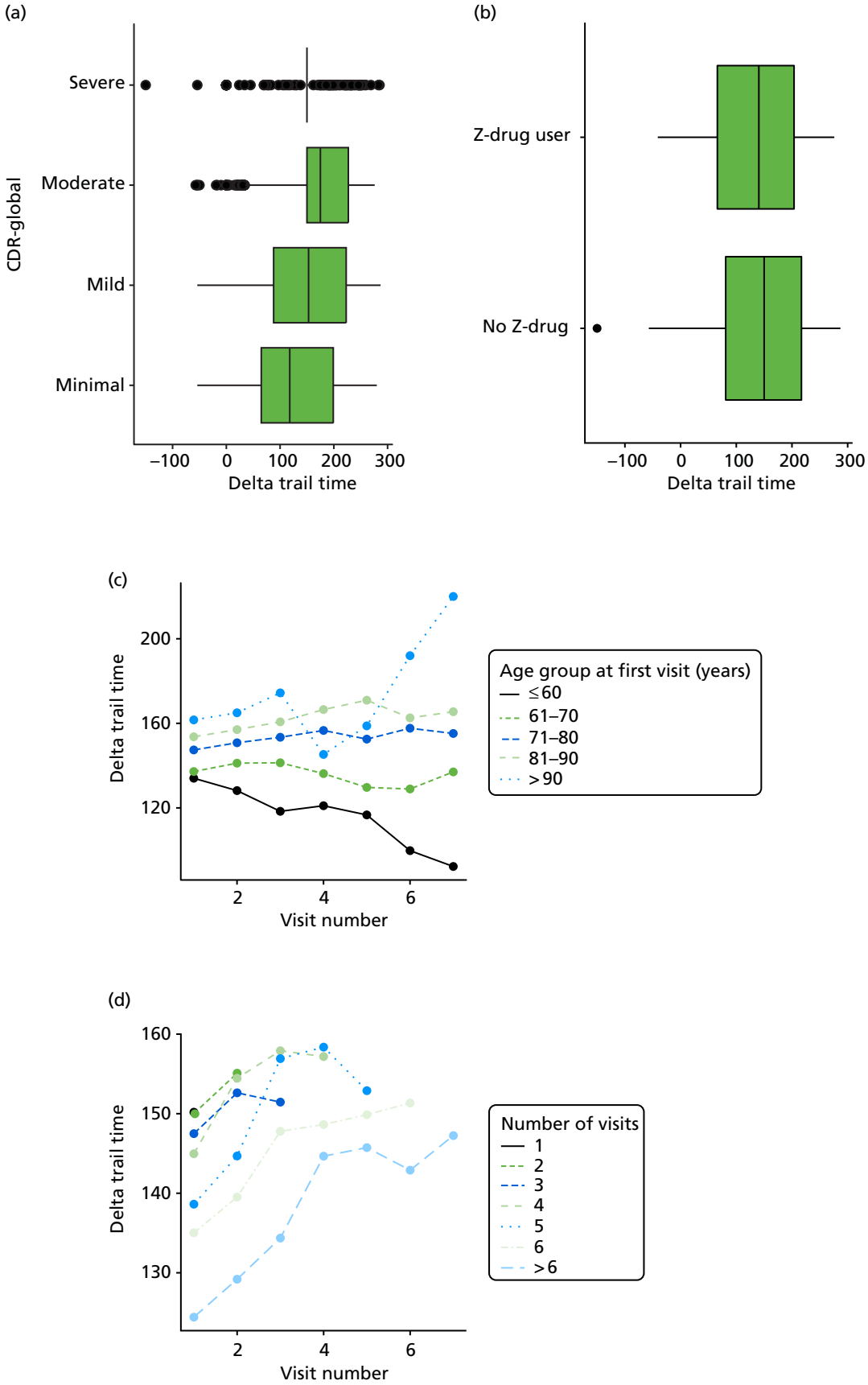

FIGURE 26 (a) Distribution of delta trail time with respect to dementia severity; (b) distribution of delta trail time with respect to Z-drug use; (c) mean score over NACC visit, stratified by age group; and (d) mean score over NACC visit, stratified by number of visits completed.

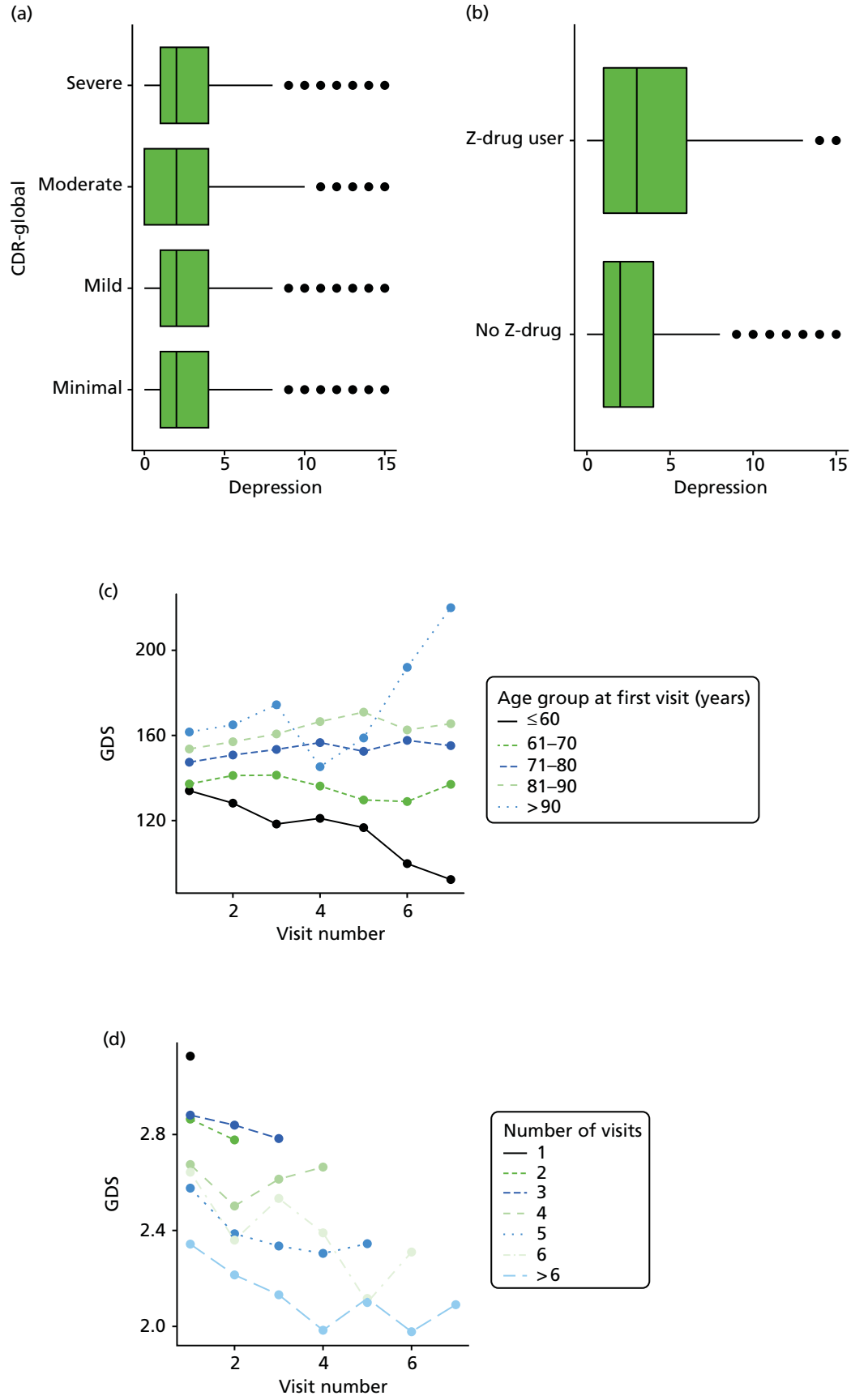

FIGURE 27 (a) Distribution of GDS with respect to dementia severity; (b) distribution of GDS with respect to Z-drug use; (c) mean score over NACC visit, stratified by age group; and (d) mean score over NACC visit, stratified by number of visits completed.

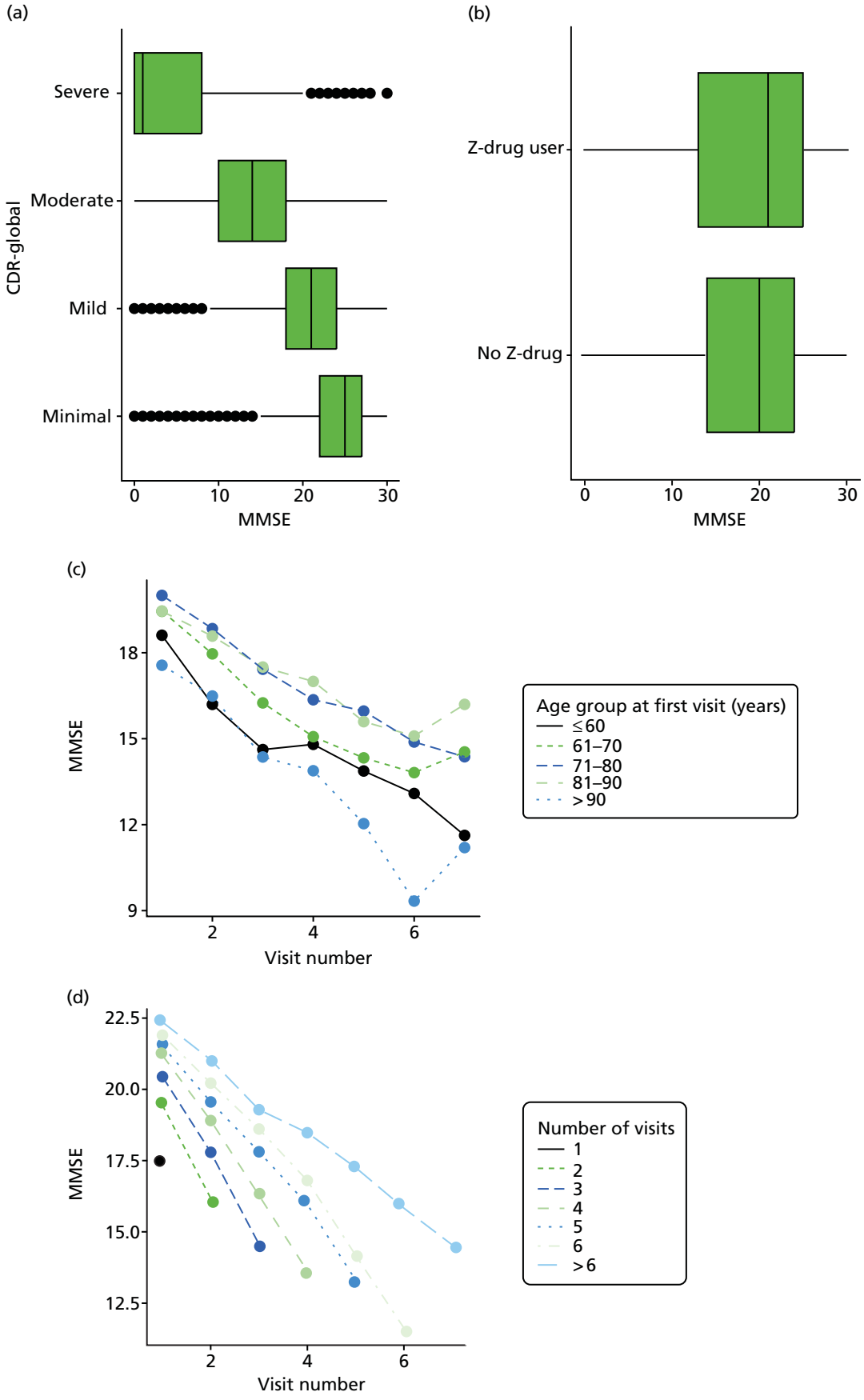

FIGURE 28 (a) Distribution of MMSE with respect to dementia severity; (b) distribution of MMSE with respect to Z-drug use; (c) mean score over NACC visit, stratified by age group; and (d) mean score over NACC visit, stratified by number of visits completed.

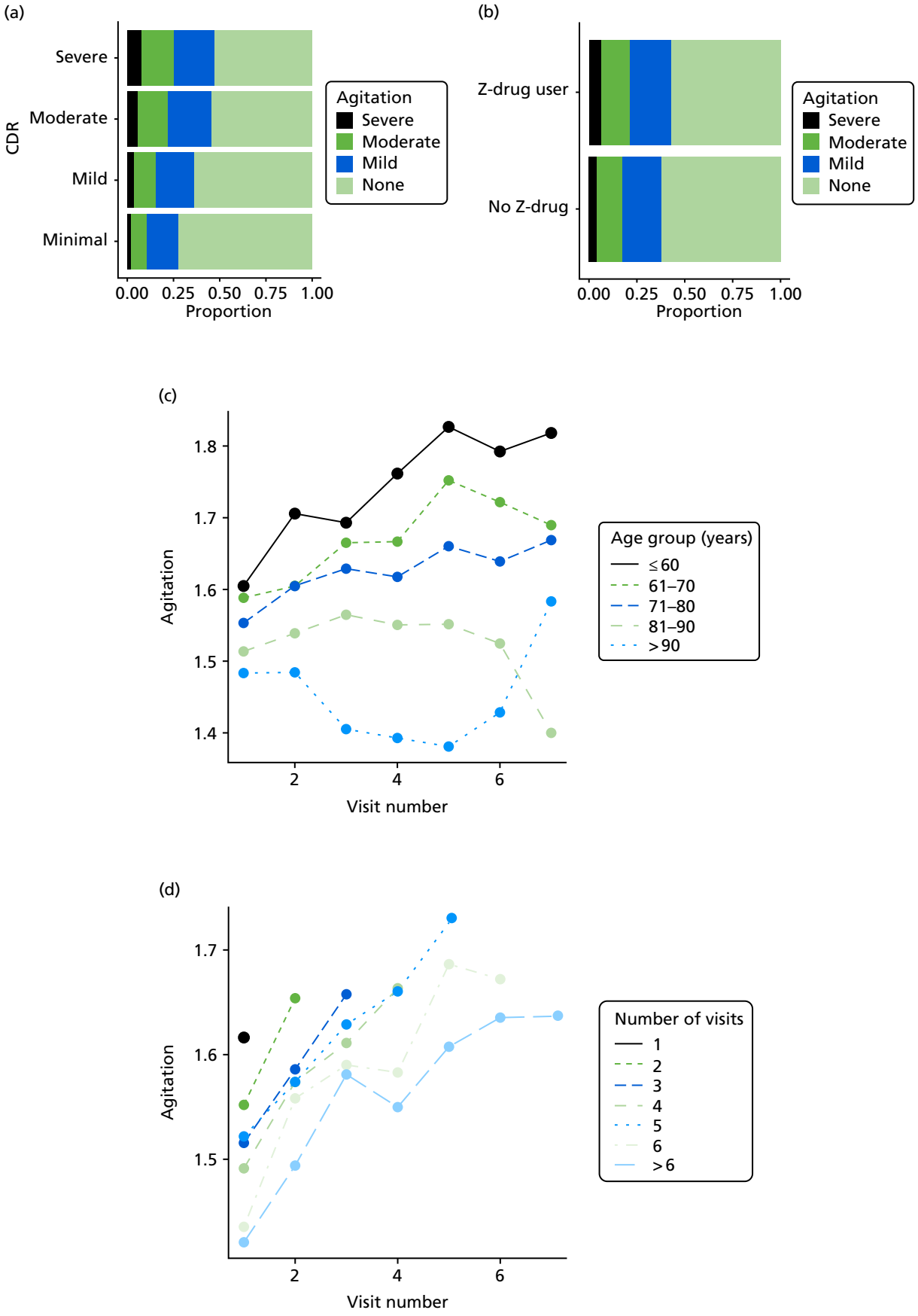

FIGURE 29 (a) Distribution of agitation with respect to dementia severity; (b) distribution of agitation with respect to Z-drug use; (c) mean score over NACC visit, stratified by age group; and (d) mean score over NACC visit, stratified by number of visits completed.

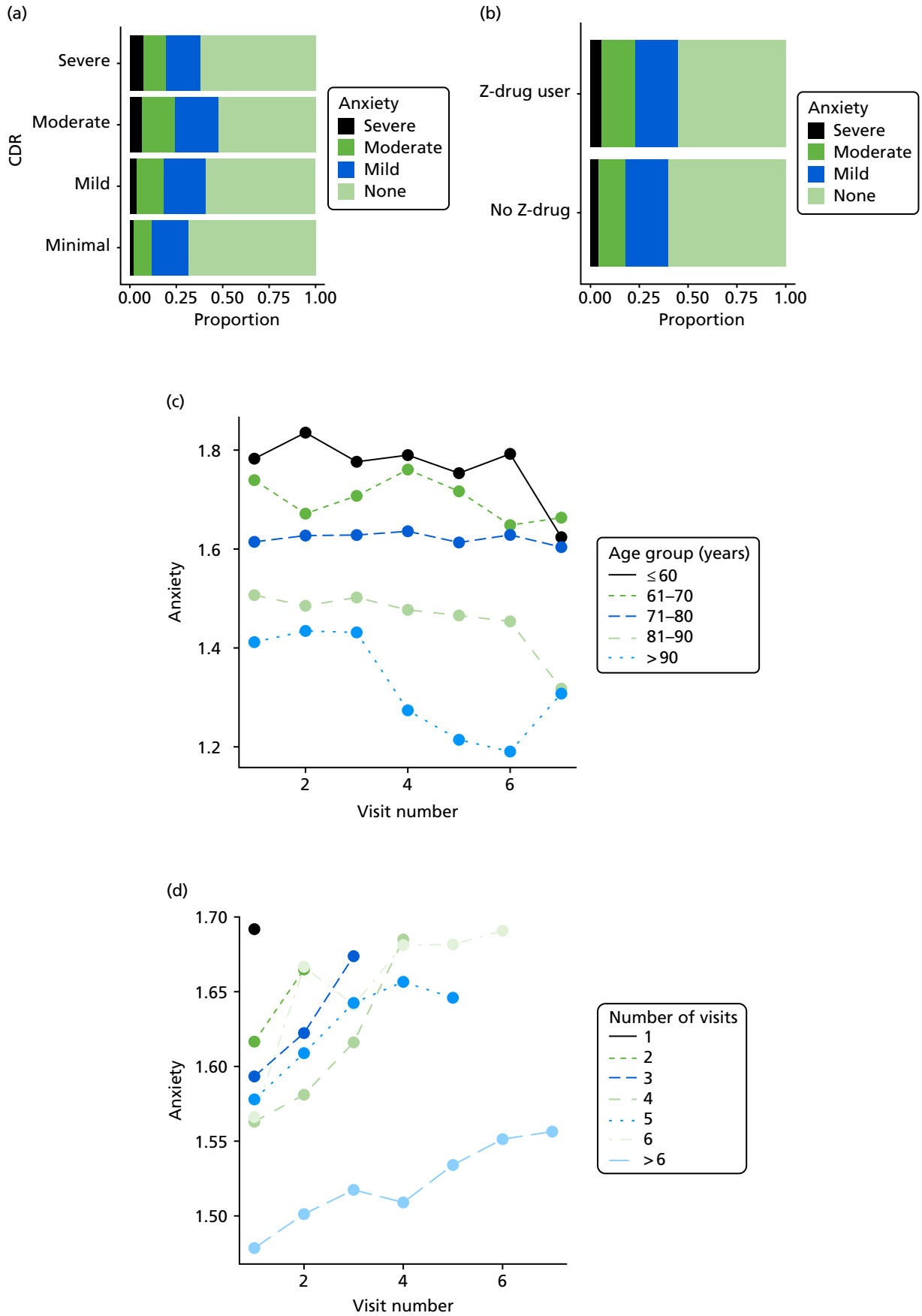

FIGURE 30 (a) Distribution of anxiety with respect to dementia severity; (b) distribution of anxiety with respect to Z-drug use; (c) mean score over NACC visit, stratified by age group; and (d) mean score over NACC visit, stratified by number of visits completed.

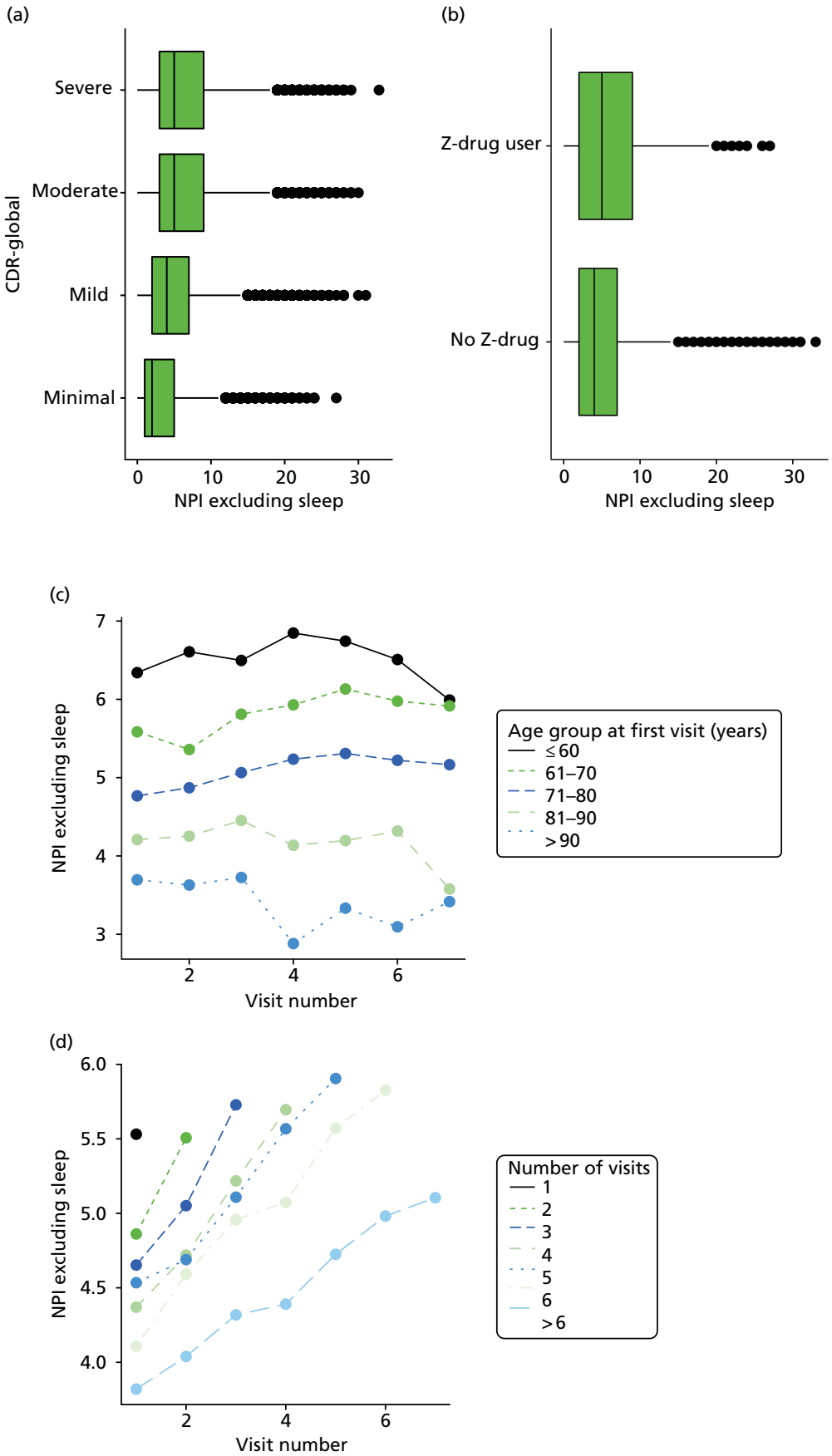

FIGURE 31 (a) Distribution of NPI (excluding sleep) with respect to dementia severity; (b) distribution of NPI (excluding sleep) with respect to Z-drug use; (c) mean score over NACC visit, stratified by age group; and (d) mean score over NACC visit, stratified by number of visits completed.

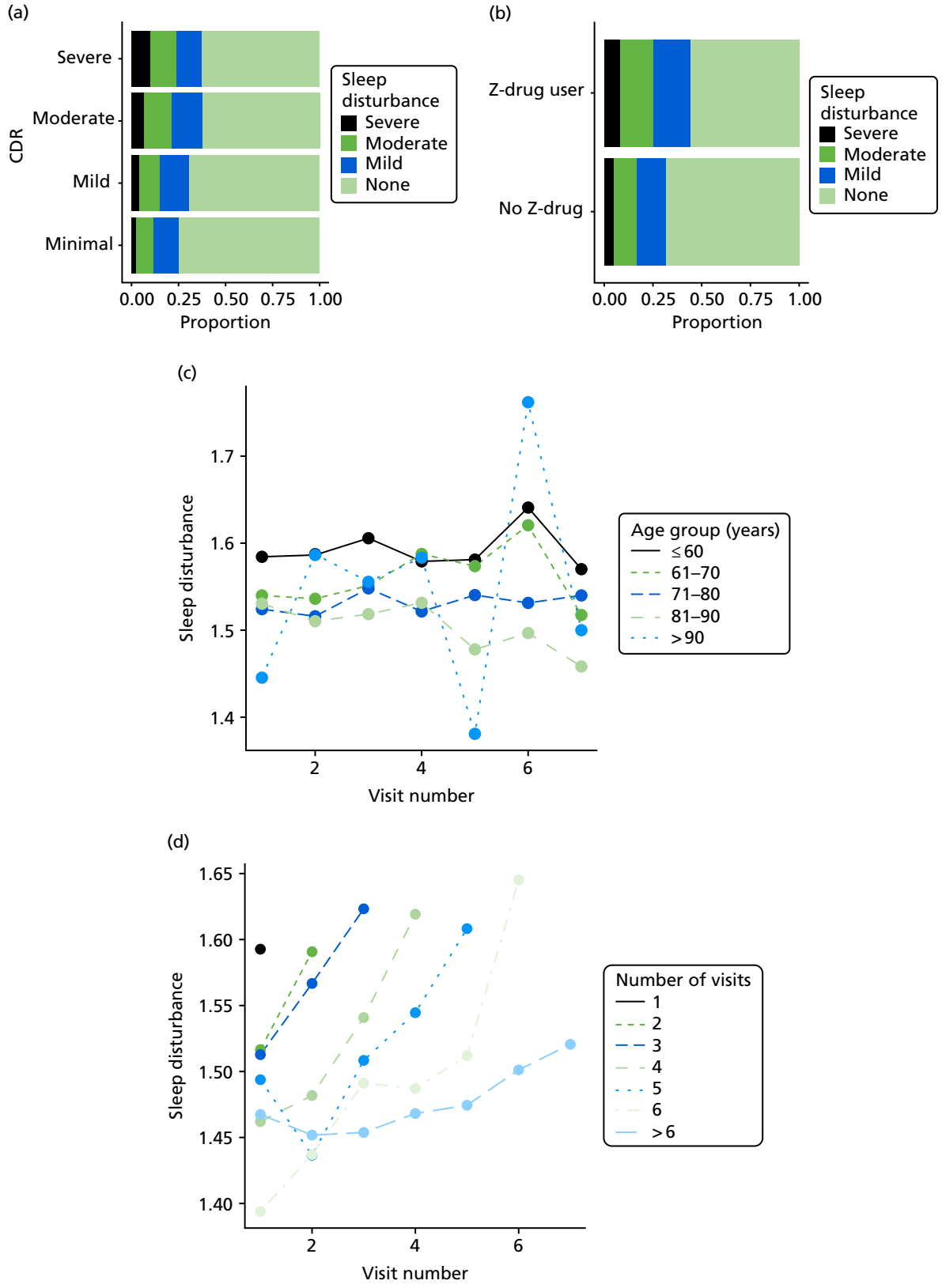

FIGURE 32 (a) Distribution of sleep disturbance with respect to dementia severity; (b) distribution of sleep disturbance with respect to Z-drug use; (c) mean score over NACC visit, stratified by age group; and (d) mean score over NACC visit, stratified by number of visits completed.

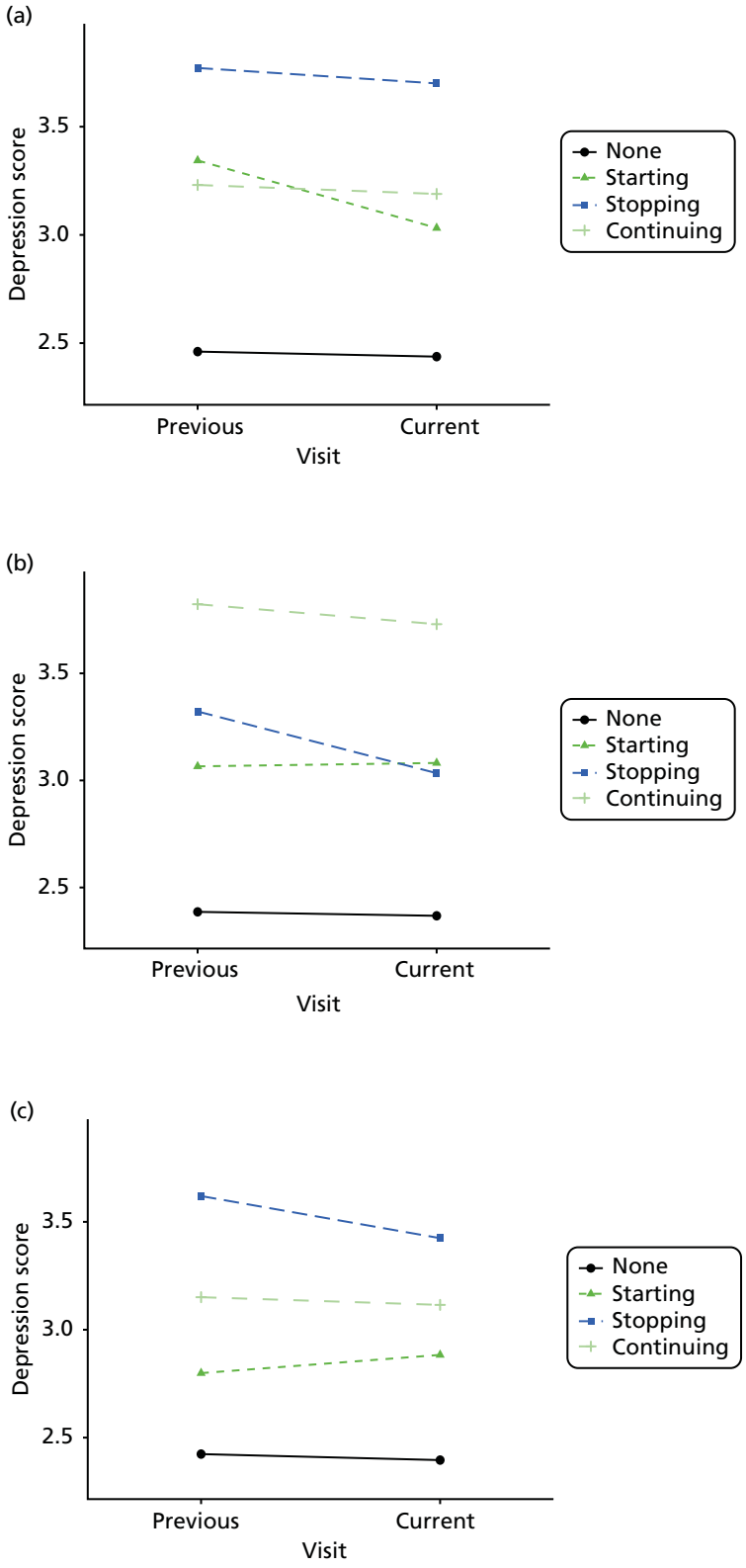

FIGURE 33 Association between changing hypnotic use status between previous and current visit on depression (measured by GDS, higher scores represent more depressive symptoms) scores at previous and current visit (a–c). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (d–f). (a) Z-drug; (b) BZD; and (c) antipsychotics. Data from the NACC data set. (*continued*)

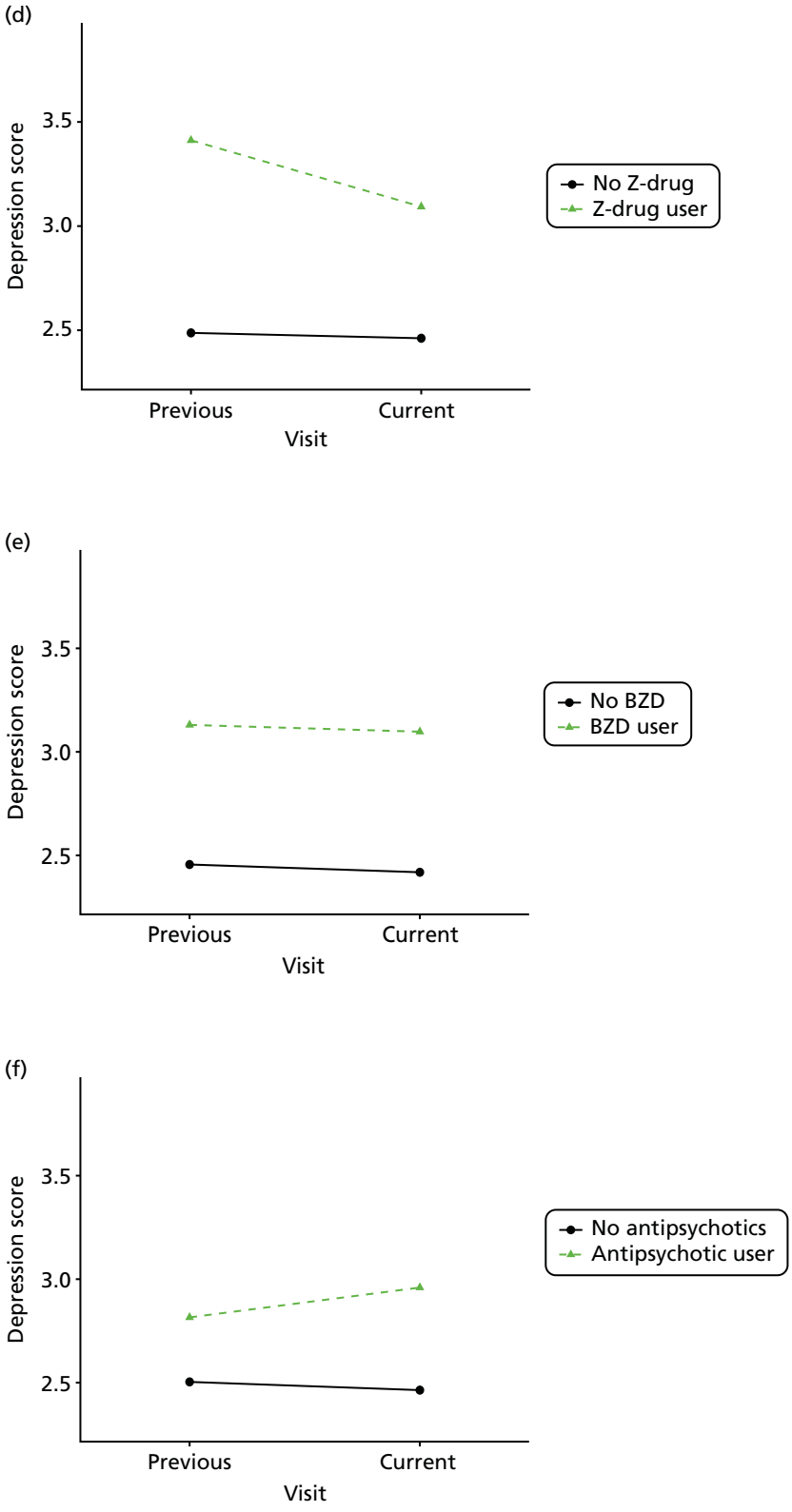

FIGURE 33 Association between changing hypnotic use status between previous and current visit on depression (measured by GDS, higher scores represent more depressive symptoms) scores at previous and current visit (a–c). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (d–f). (a) Z-drug; (b) BZD; and (c) antipsychotics. Data from the NACC data set.

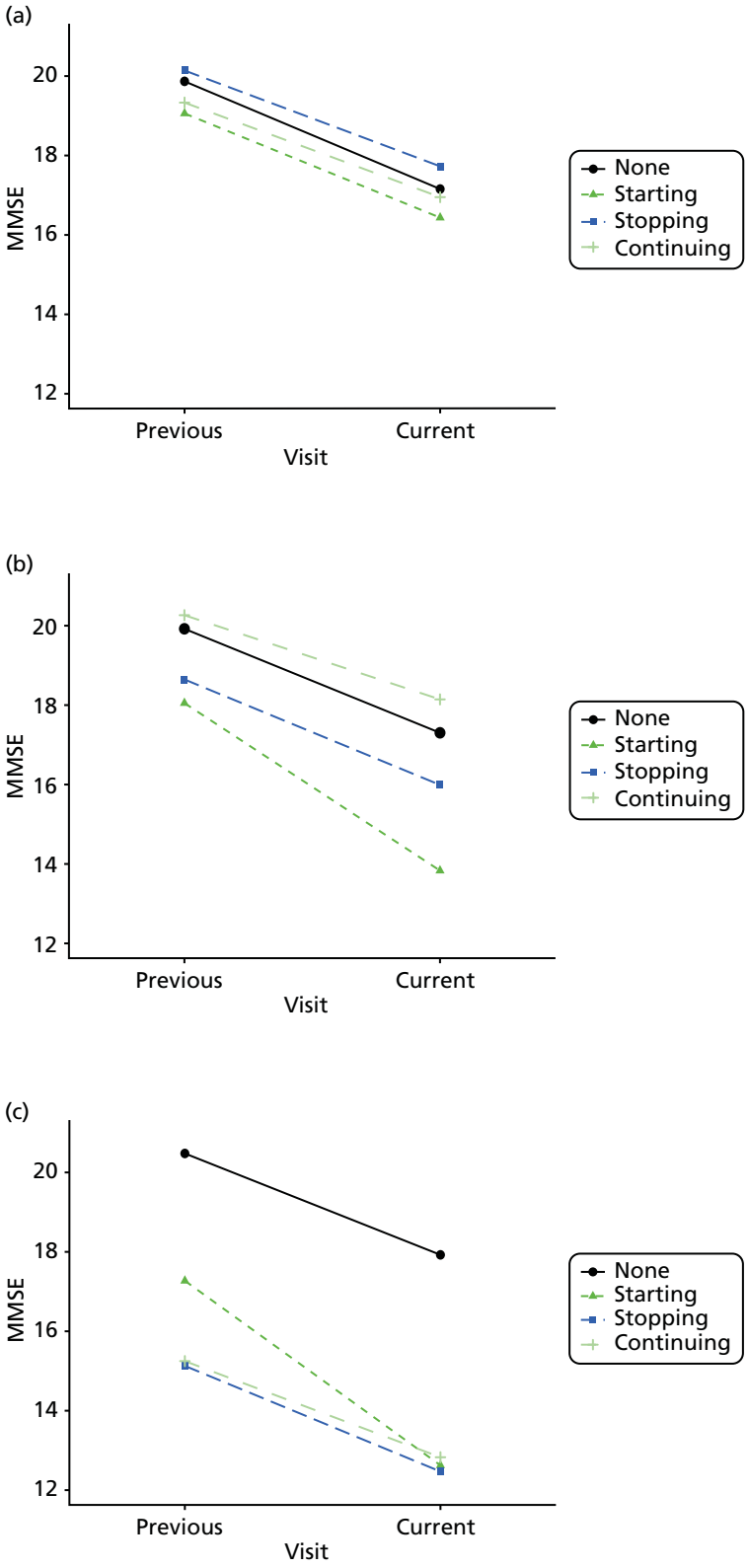

FIGURE 34 Association between changing hypnotic use status between previous and current visit on MMSE scores (higher scores represent better cognitive function) at previous and current visit (a–c). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (d–f). (a) Z-drug; (b) BZD; and (c) antipsychotics. Data from the NACC data set. (*continued*)

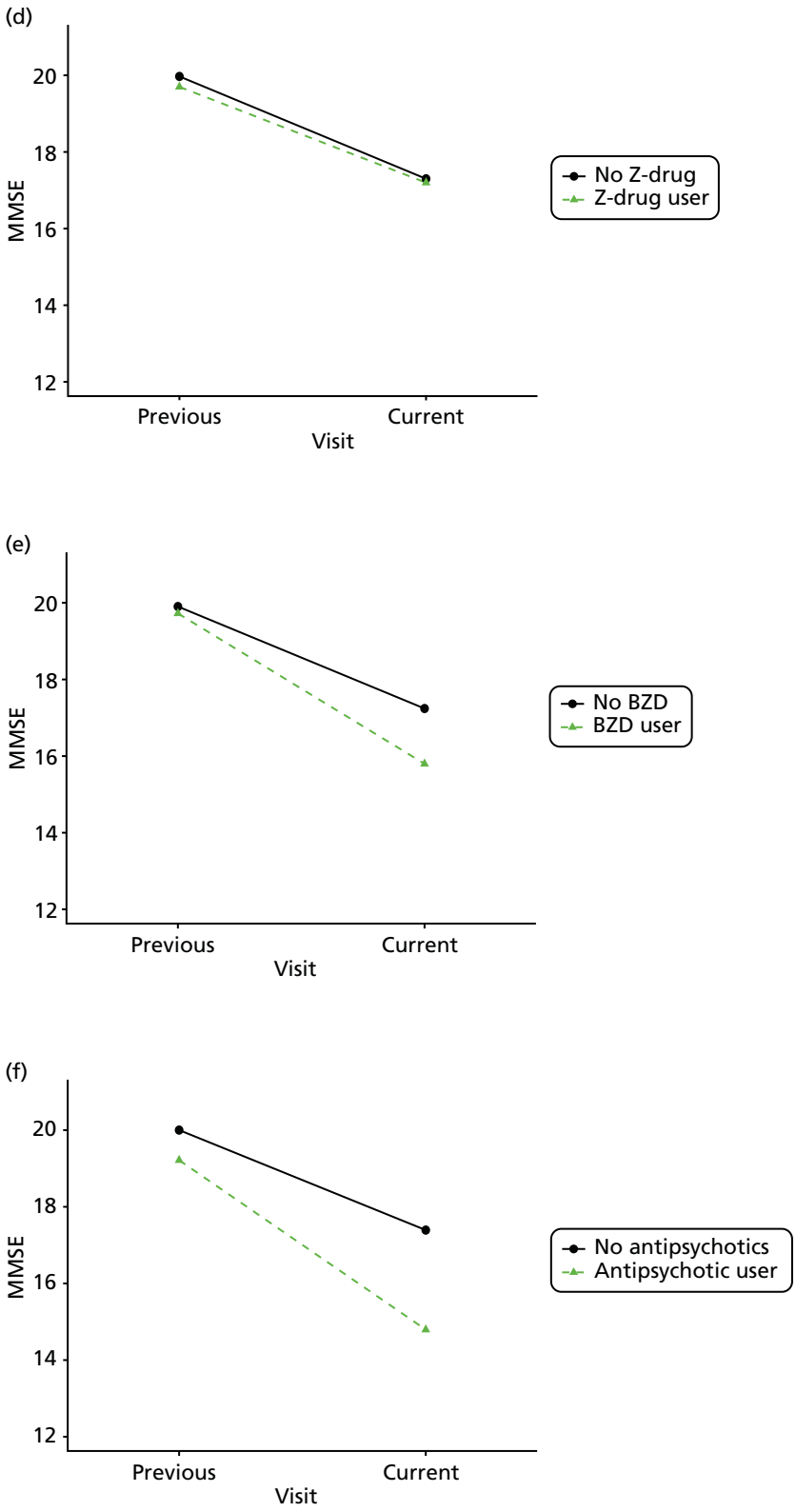

FIGURE 34 Association between changing hypnotic use status between previous and current visit on MMSE scores (higher scores represent better cognitive function) at previous and current visit (a–c). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (d–f). (a) Z-drug; (b) BZD; and (c) antipsychotics. Data from the NACC data set.

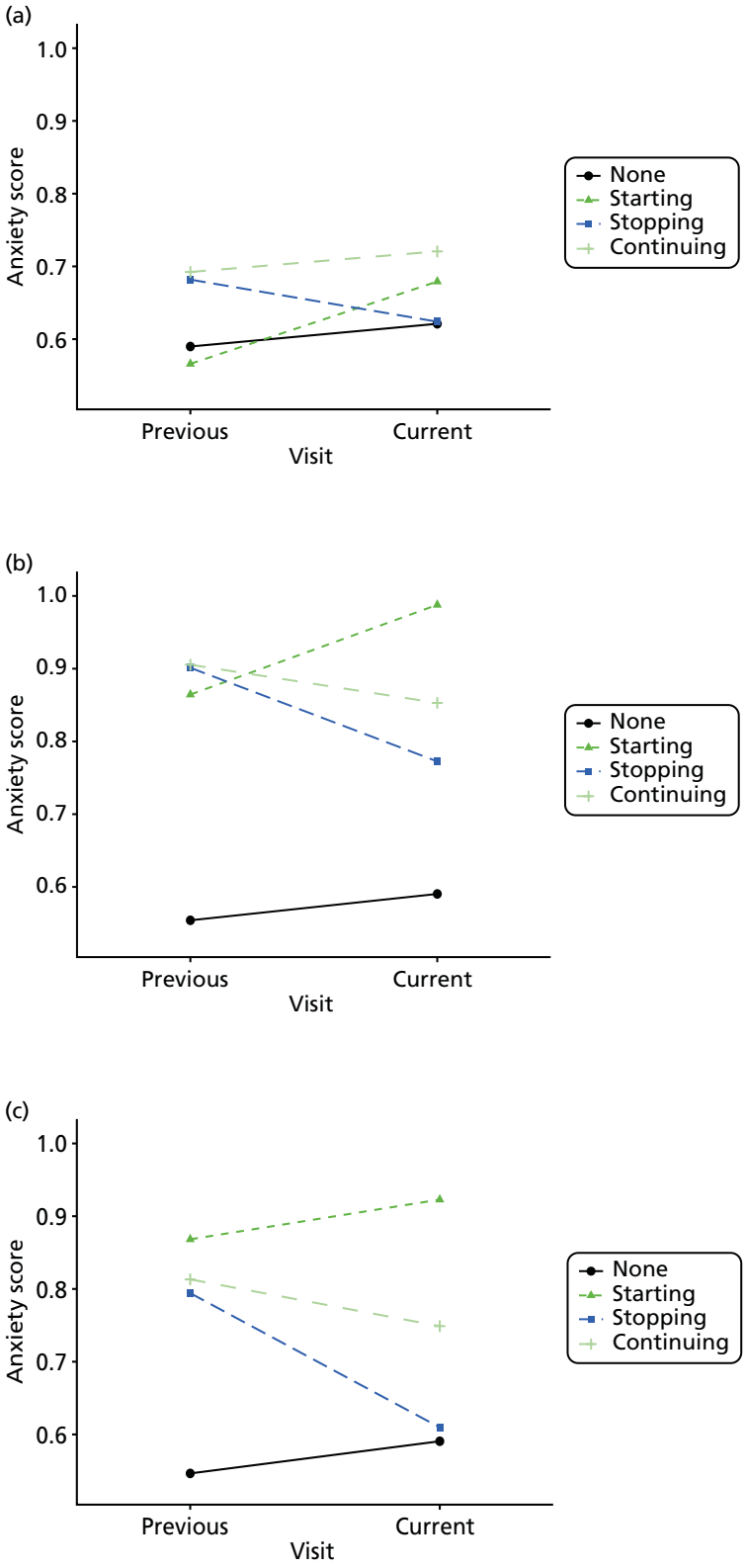

FIGURE 35 Association between changing hypnotic use status between previous and current visit on anxiety scores at previous and current visit (a–c). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (d–f). (a) Z-drug; (b) BZD; and (c) antipsychotics. Data from the NACC data set. (*continued*)

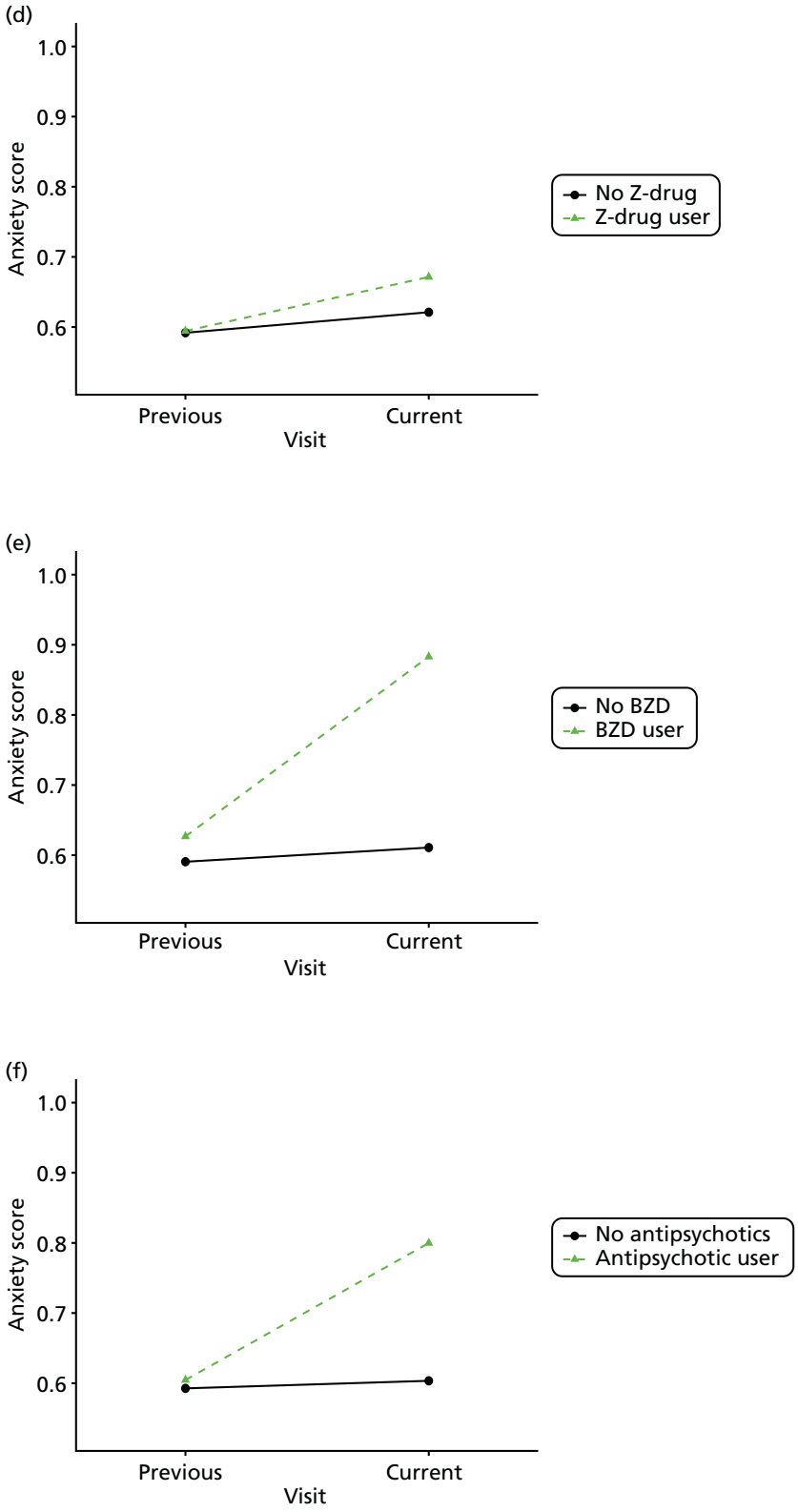

FIGURE 35 Association between changing hypnotic use status between previous and current visit on anxiety scores at previous and current visit (a–c). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (d–f). (a) Z-drug; (b) BZD; and (c) antipsychotics. Data from the NACC data set.

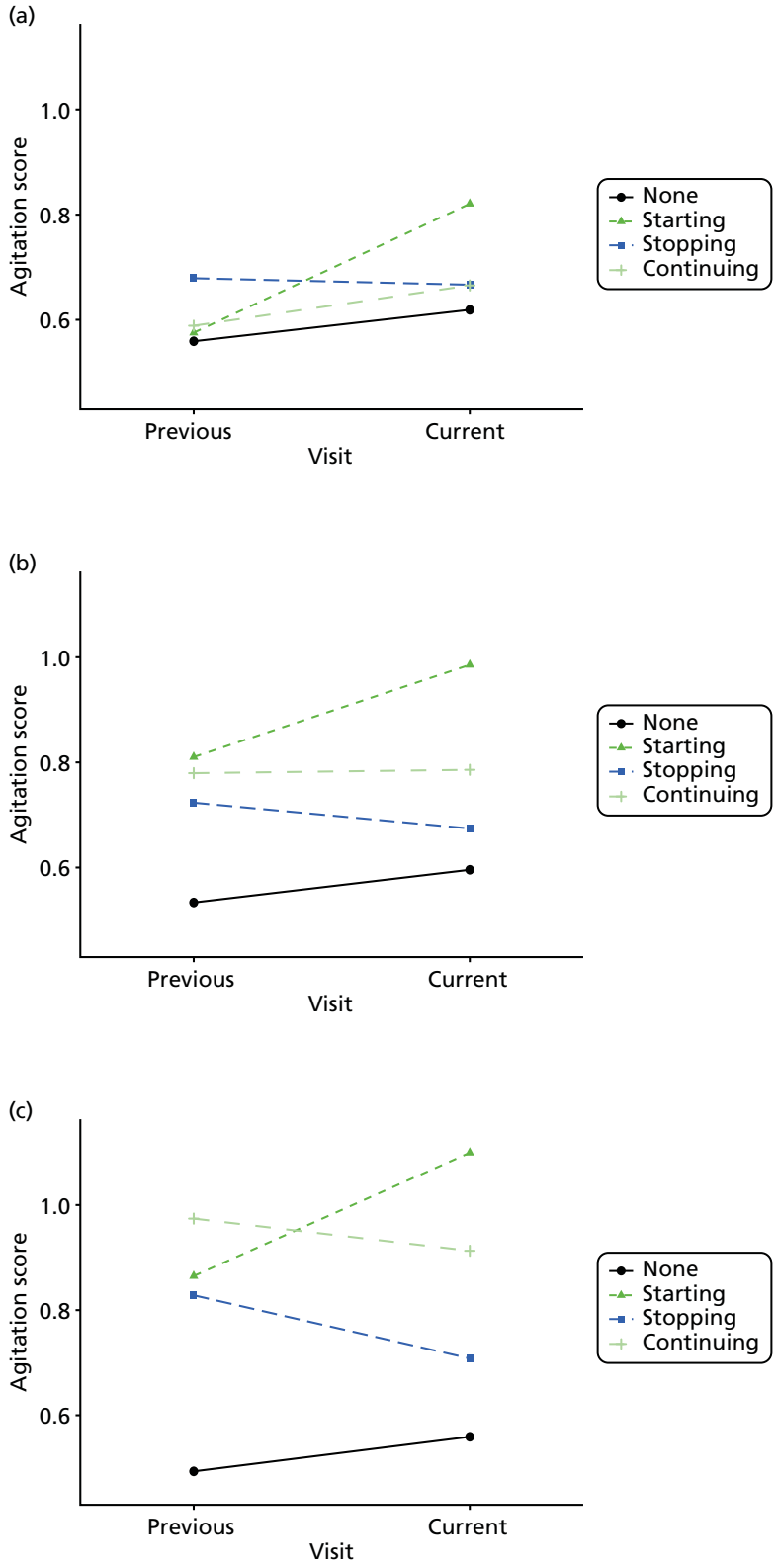

FIGURE 36 Association between changing hypnotic use status between previous and current visit on agitation scores at previous and current visit (a–c). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (d–f). (a) Z-drug; (b) BZD; and (c) antipsychotics. Data from the NACC data set. (*continued*)

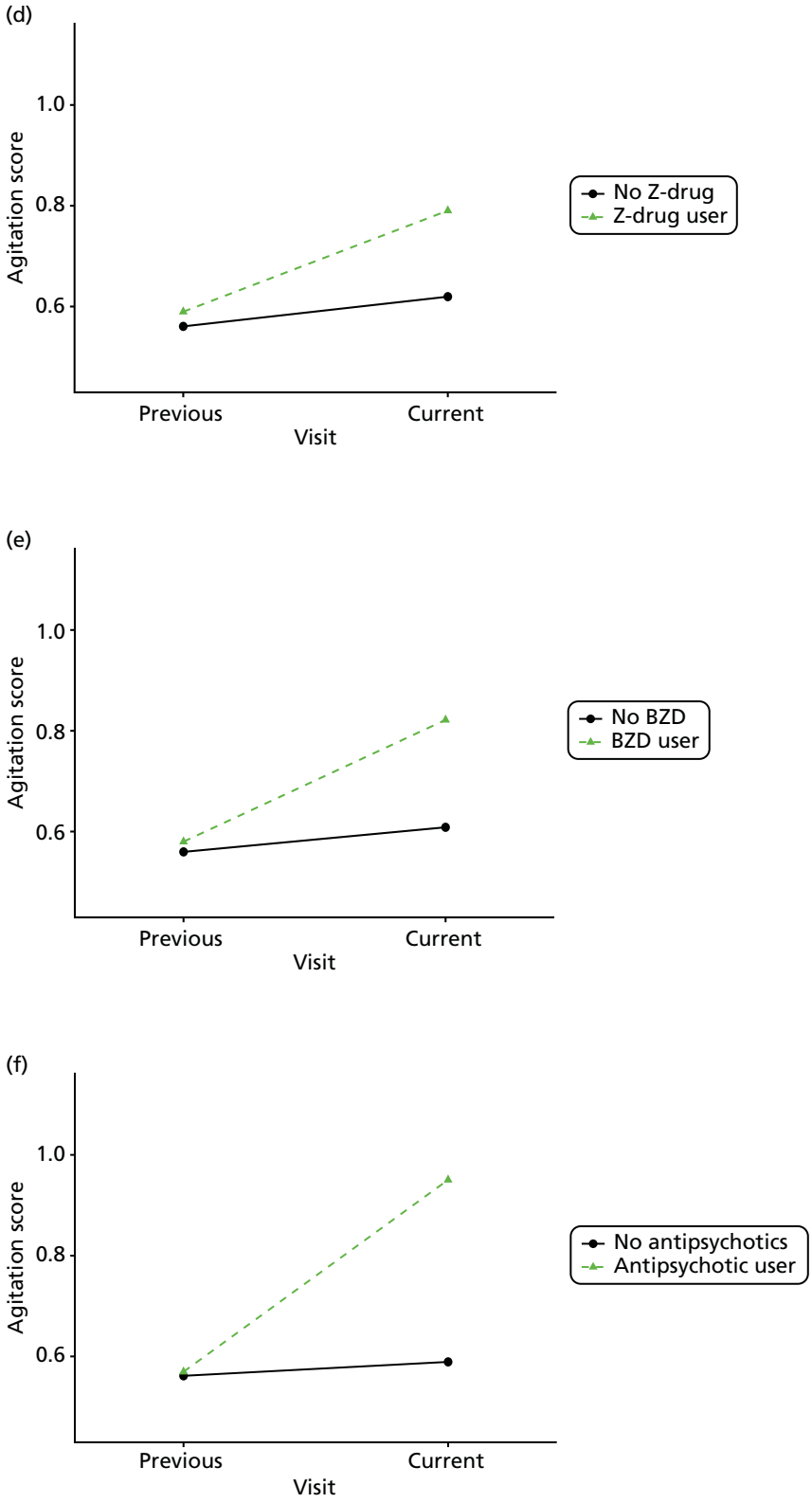

FIGURE 36 Association between changing hypnotic use status between previous and current visit on agitation scores at previous and current visit (a–c). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (d–f). (a) Z-drug; (b) BZD; and (c) antipsychotics. Data from the NACC data set.

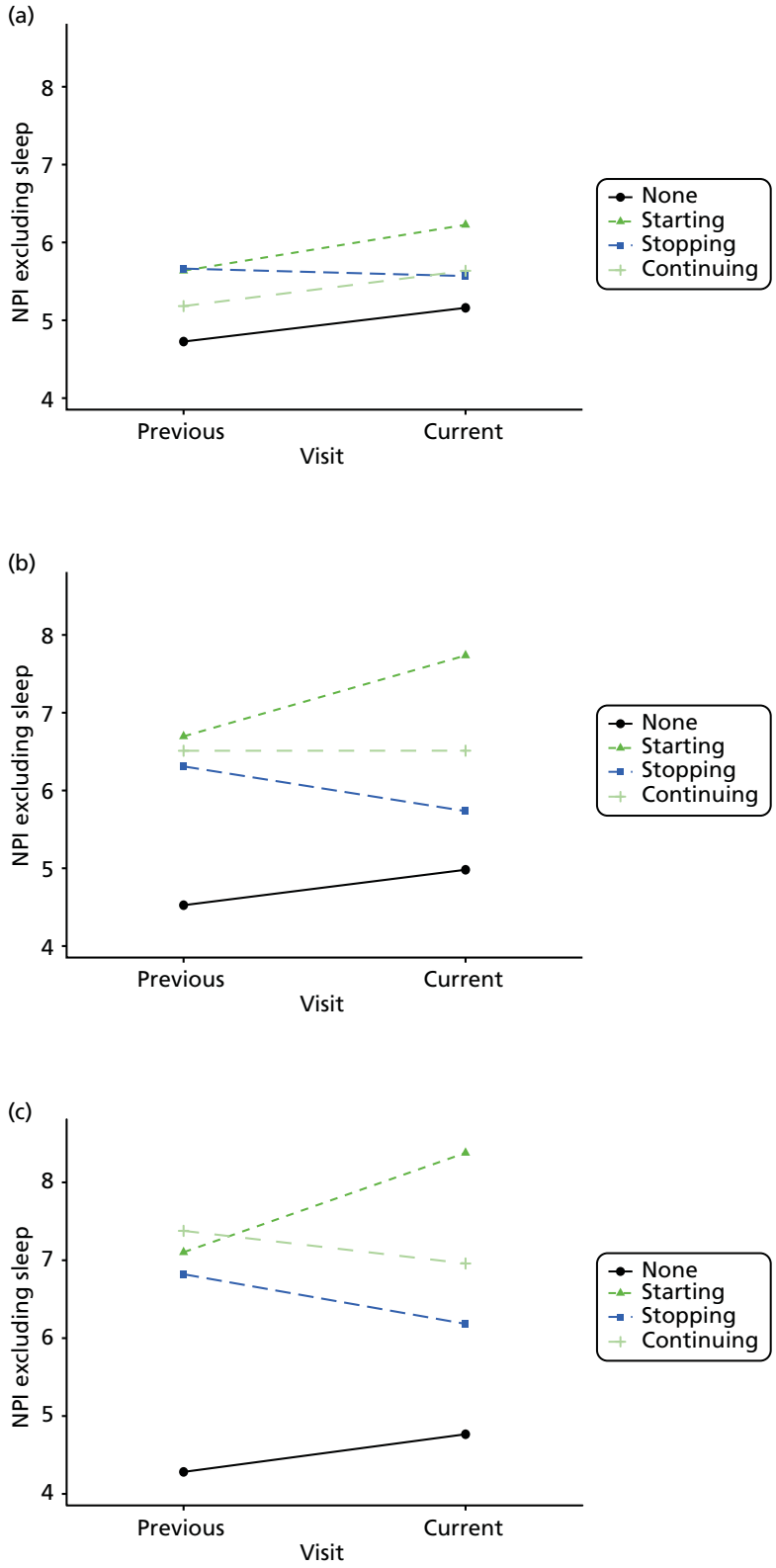

FIGURE 37 Association between changing hypnotic use status between previous and current visit on NPI (excluding sleep question) scores at previous and current visit (a–c). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (d–f). (a) Z-drug; (b) BZD; and (c) antipsychotics. Data from the NACC data set. (*continued*)

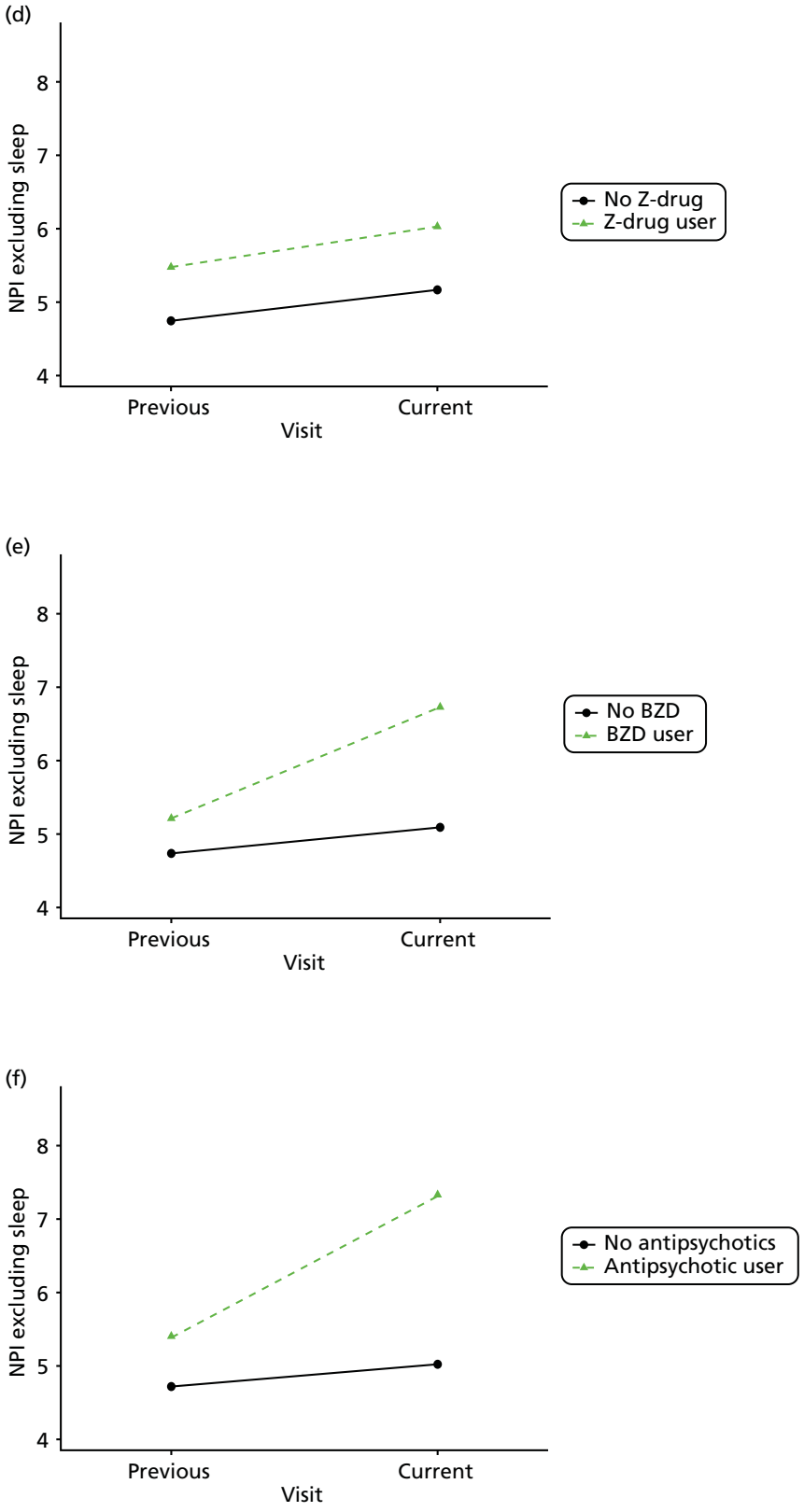

FIGURE 37 Association between changing hypnotic use status between previous and current visit on NPI (excluding sleep question) scores at previous and current visit (a–c). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (d–f). (a) Z-drug; (b) BZD; and (c) antipsychotics. Data from the NACC data set.

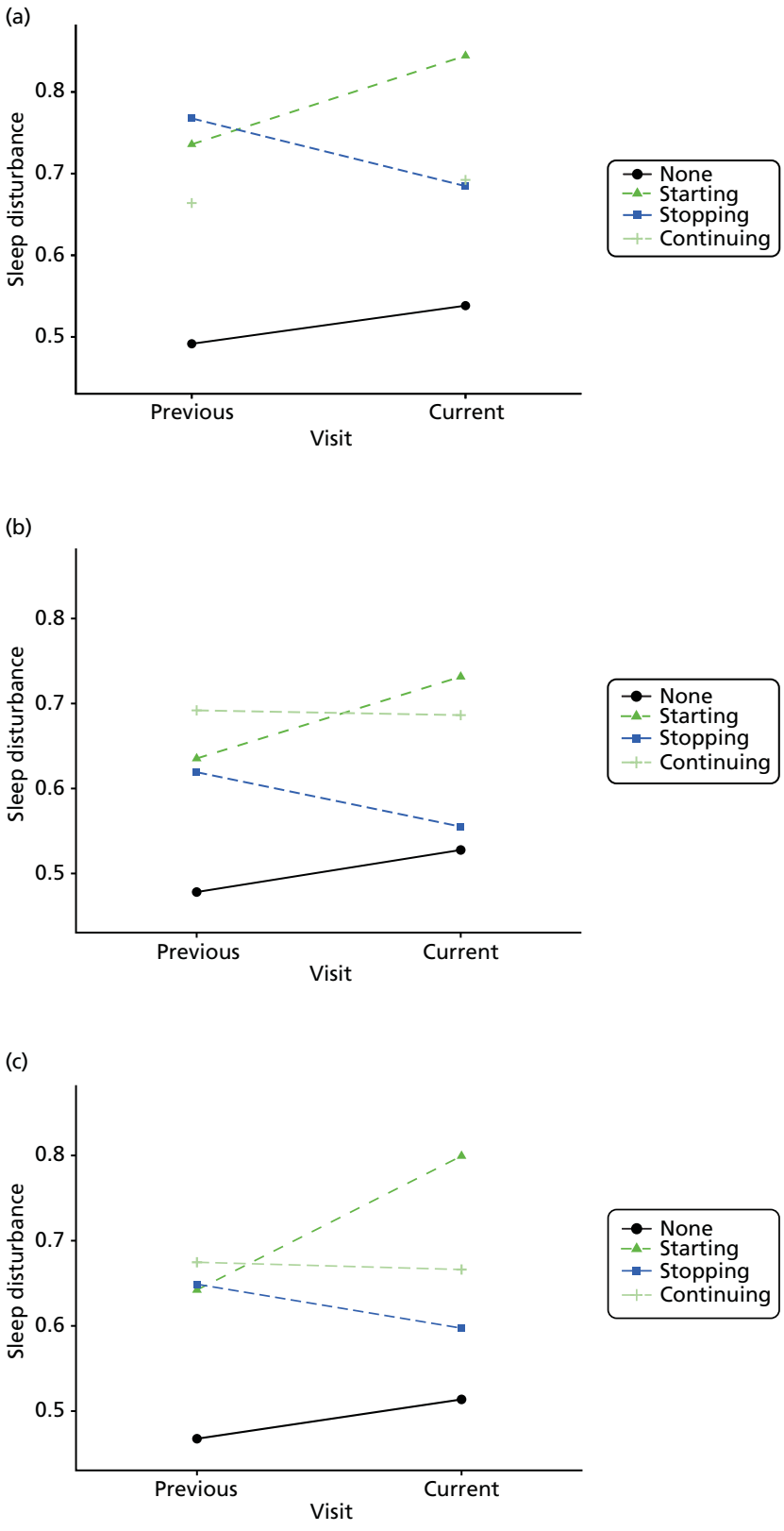

FIGURE 38 Association between changing hypnotic use status between previous and current visit on NPI sleep disturbance scores at previous and current visit (a–c). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (d–f). (a) Z-drug; (b) BZD; and (c) antipsychotics. Data from the NACC data set. (*continued*)

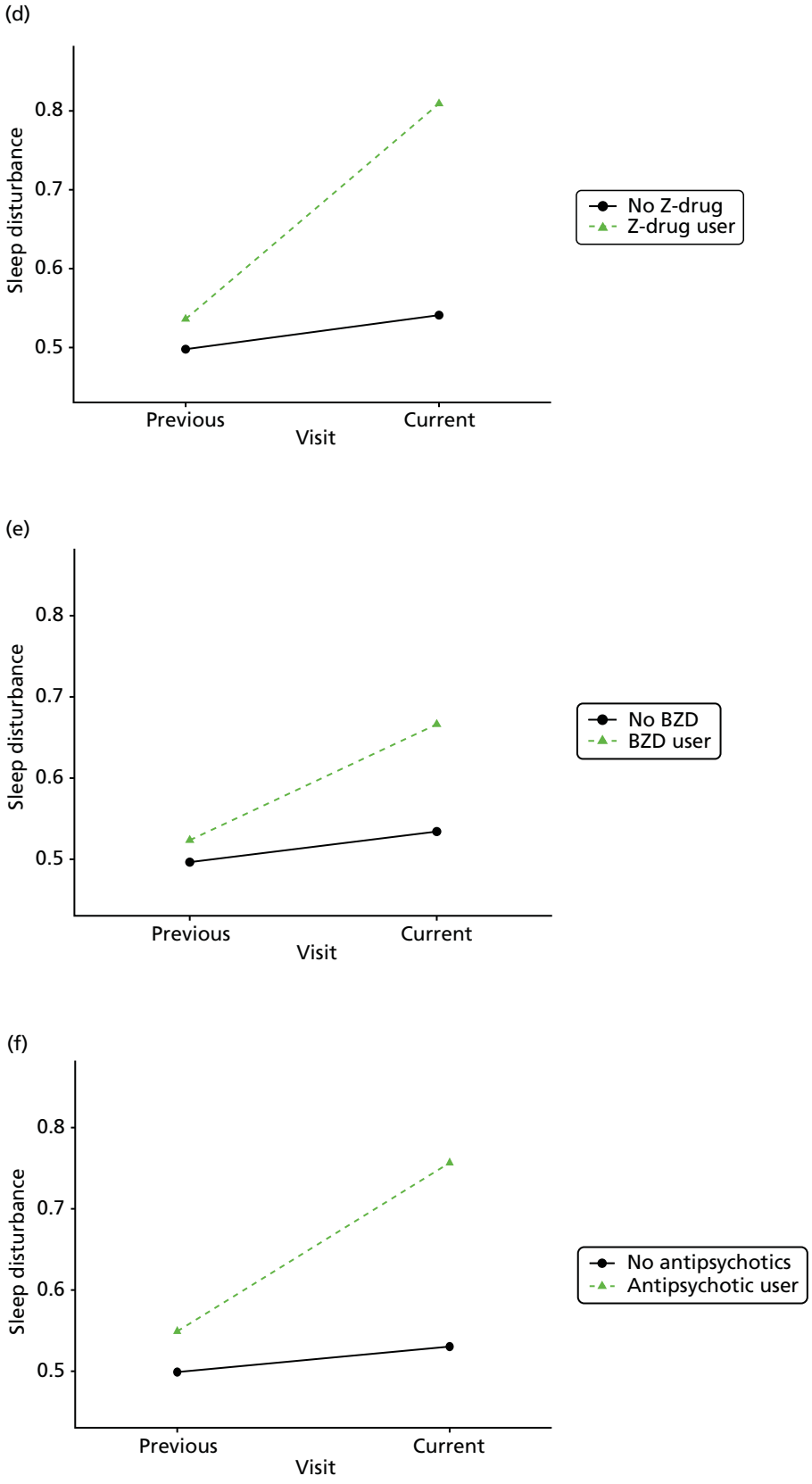

FIGURE 38 Association between changing hypnotic use status between previous and current visit on NPI sleep disturbance scores at previous and current visit (a–c). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (d–f). (a) Z-drug; (b) BZD; and (c) antipsychotics. Data from the NACC data set.

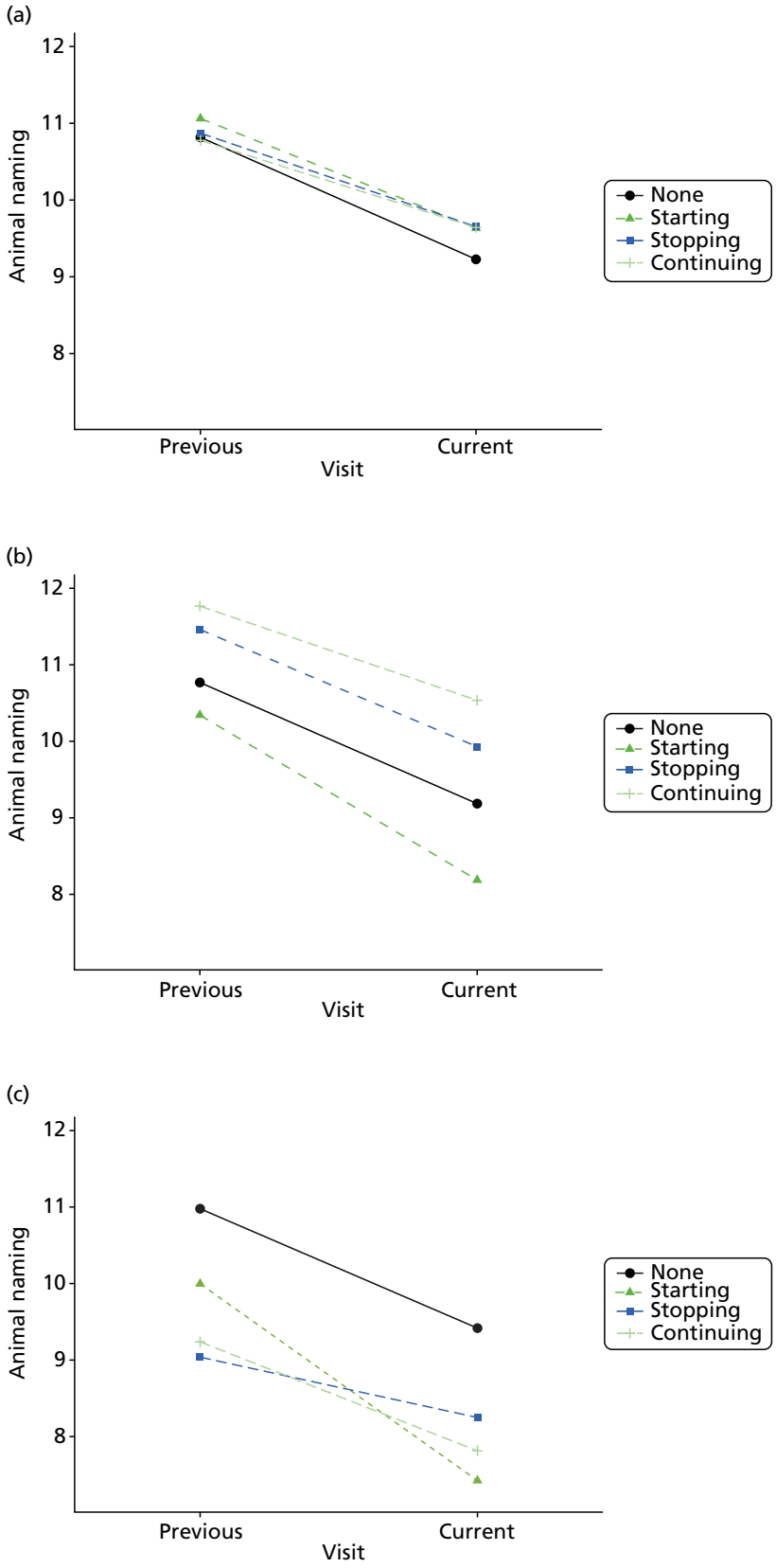

FIGURE 39 Association between changing hypnotic use status between previous and current visit on animal fluency scores (higher scores represent better cognitive function) at previous and current visit (a–c). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (d–f). (a) Z-drug; (b) BZD; and (c) antipsychotics. Data from the NACC data set. (*continued*)

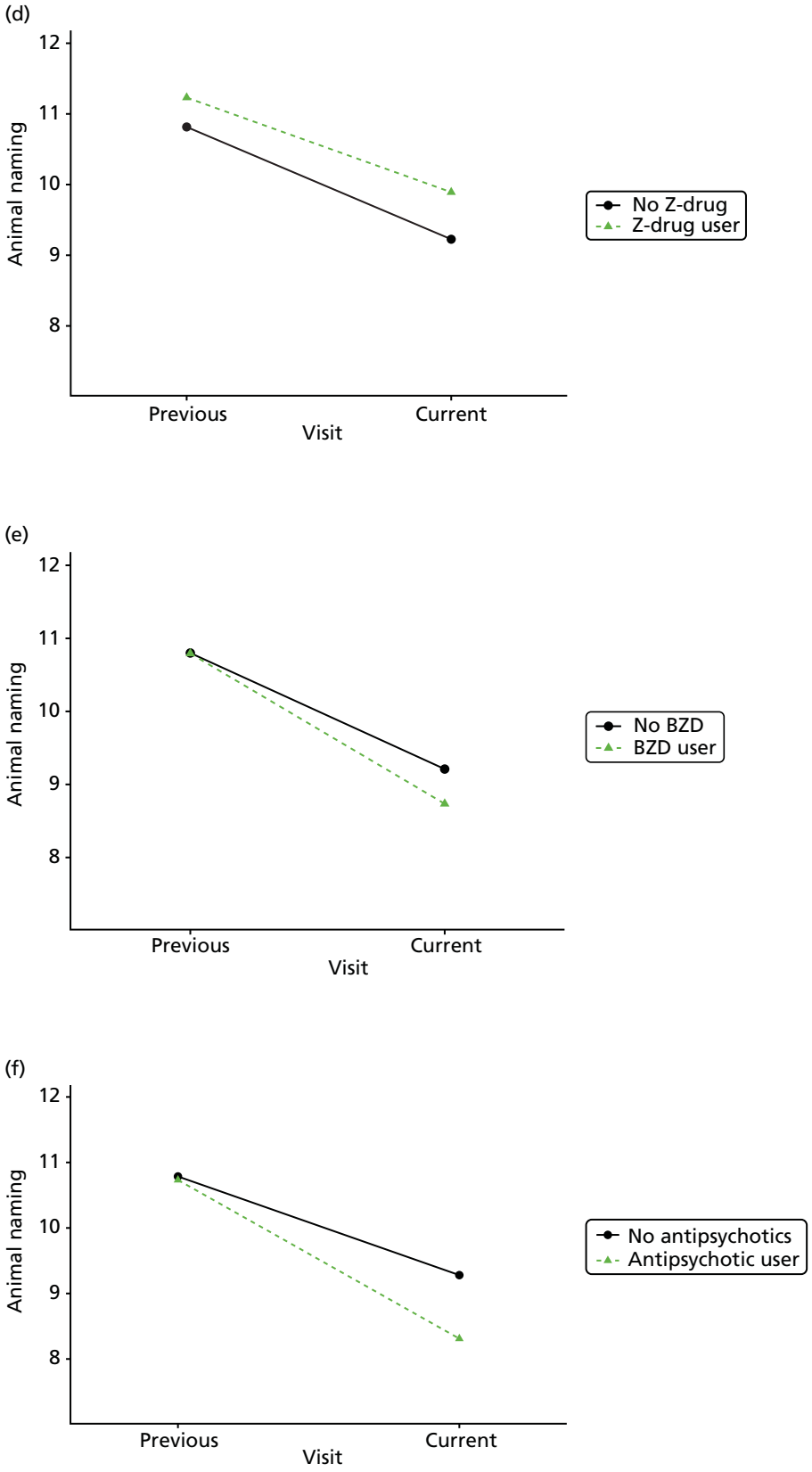

FIGURE 39 Association between changing hypnotic use status between previous and current visit on animal fluency scores (higher scores represent better cognitive function) at previous and current visit (a–c). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (d–f). (a) Z-drug; (b) BZD; and (c) antipsychotics. Data from the NACC data set.

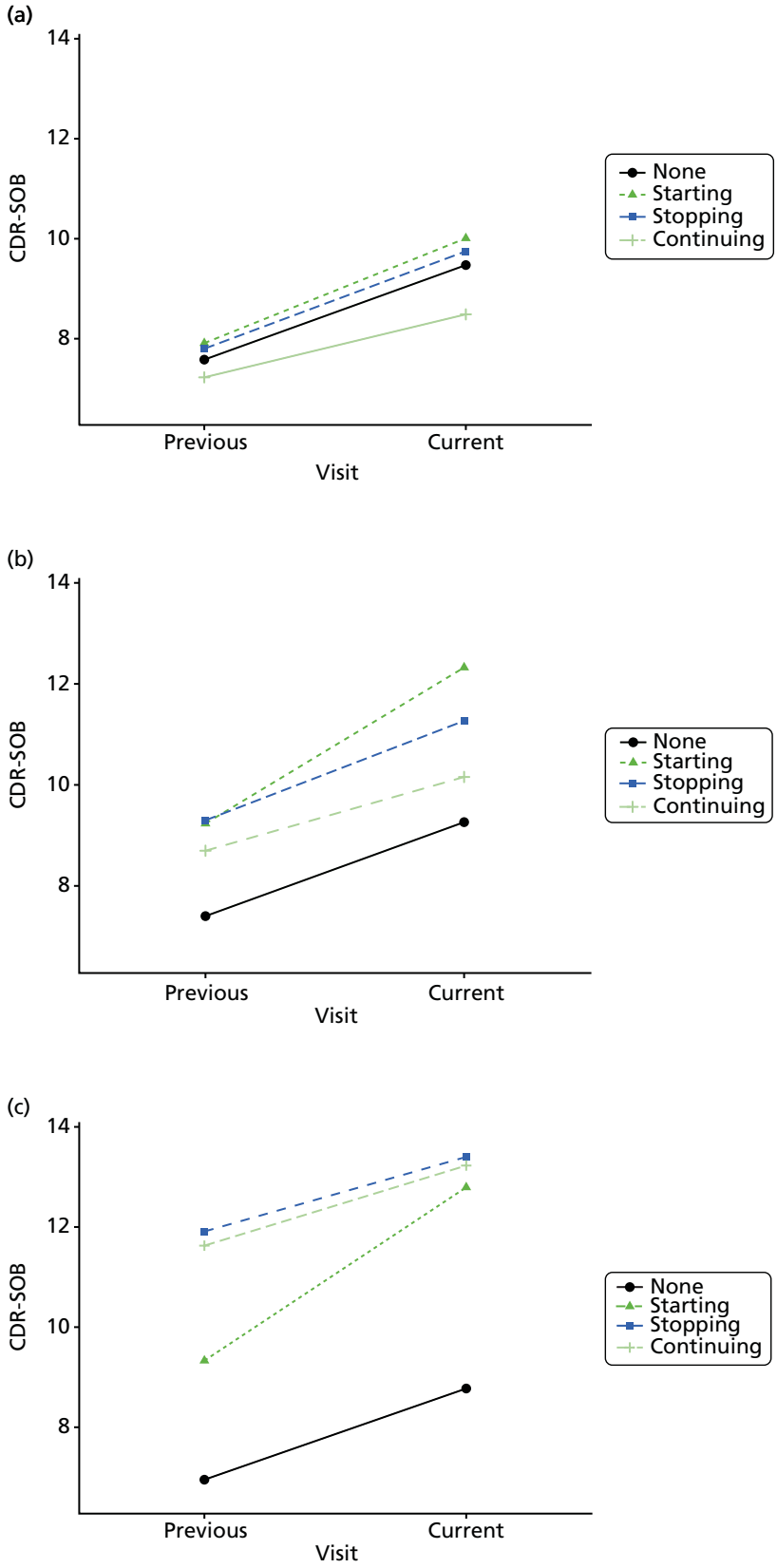

FIGURE 40 Association between changing hypnotic use status between previous and current visit on CDR-SOB scores (higher scores represent more cognitive impairment) at previous and current visit (a–c). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (d–f). (a) Z-drug; (b) BZD; and (c) antipsychotics. Data from the NACC data set. (*continued*)

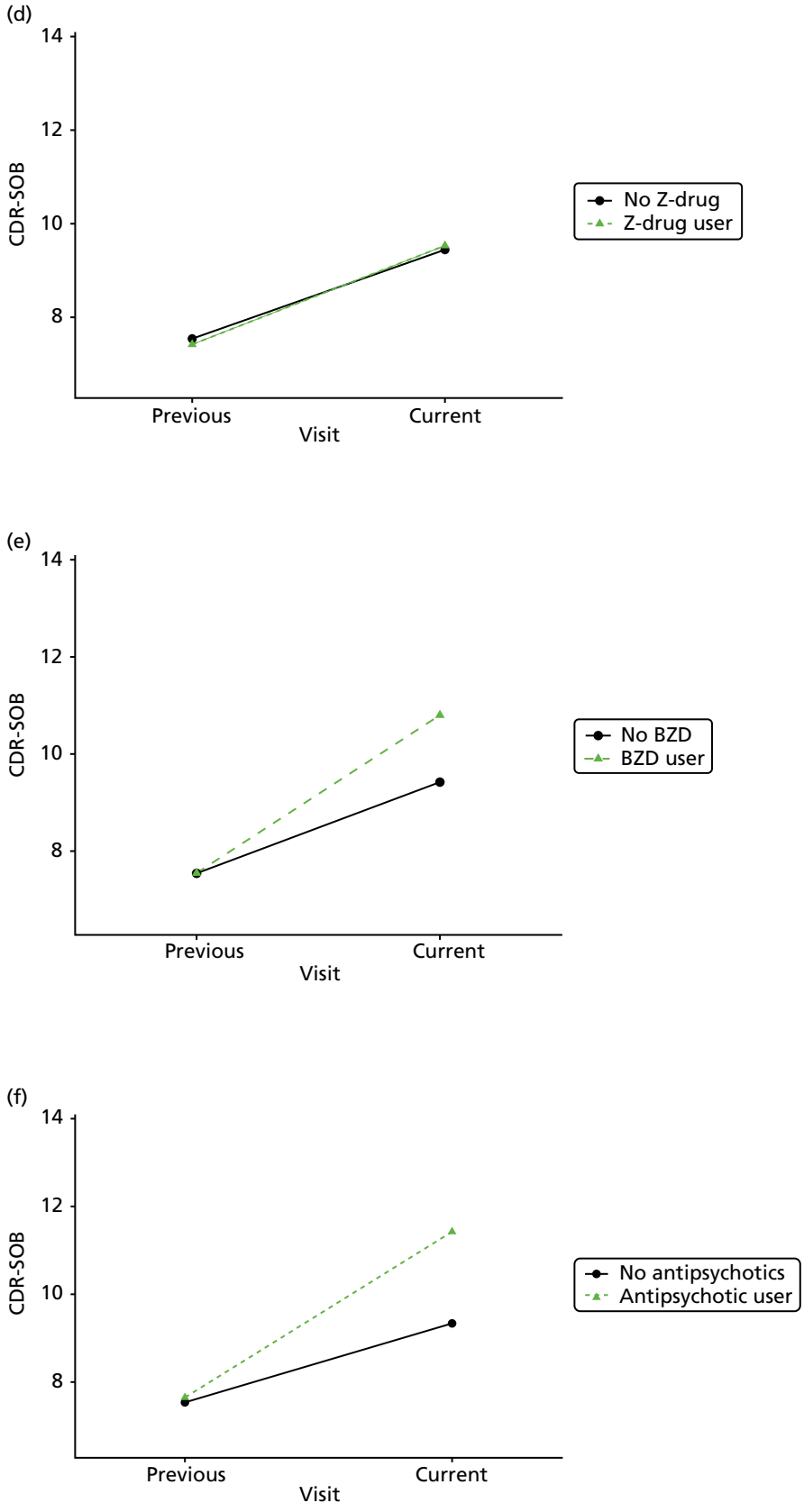

FIGURE 40 Association between changing hypnotic use status between previous and current visit on CDR-SOB scores (higher scores represent more cognitive impairment) at previous and current visit (a–c). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (d–f). (a) Z-drug; (b) BZD; and (c) antipsychotics. Data from the NACC data set.

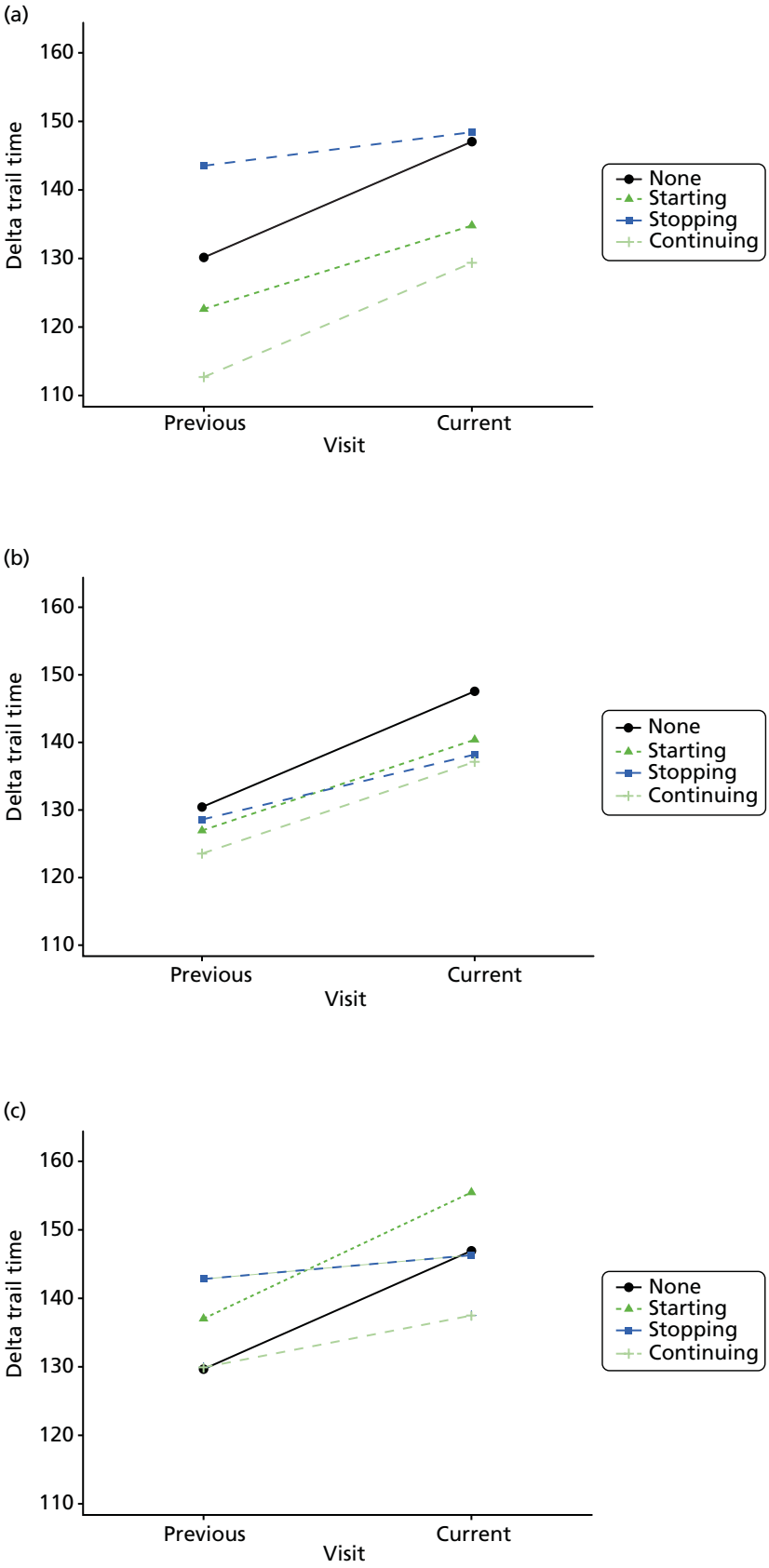

FIGURE 41 Association between changing hypnotic use status between previous and current visit on delta trail time scores (higher scores represent more cognitive impairment) at previous and current visit (a–c). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (d–f). (a) Z-drug; (b) BZD; and (c) antipsychotics. Data from the NACC data set. (*continued*)

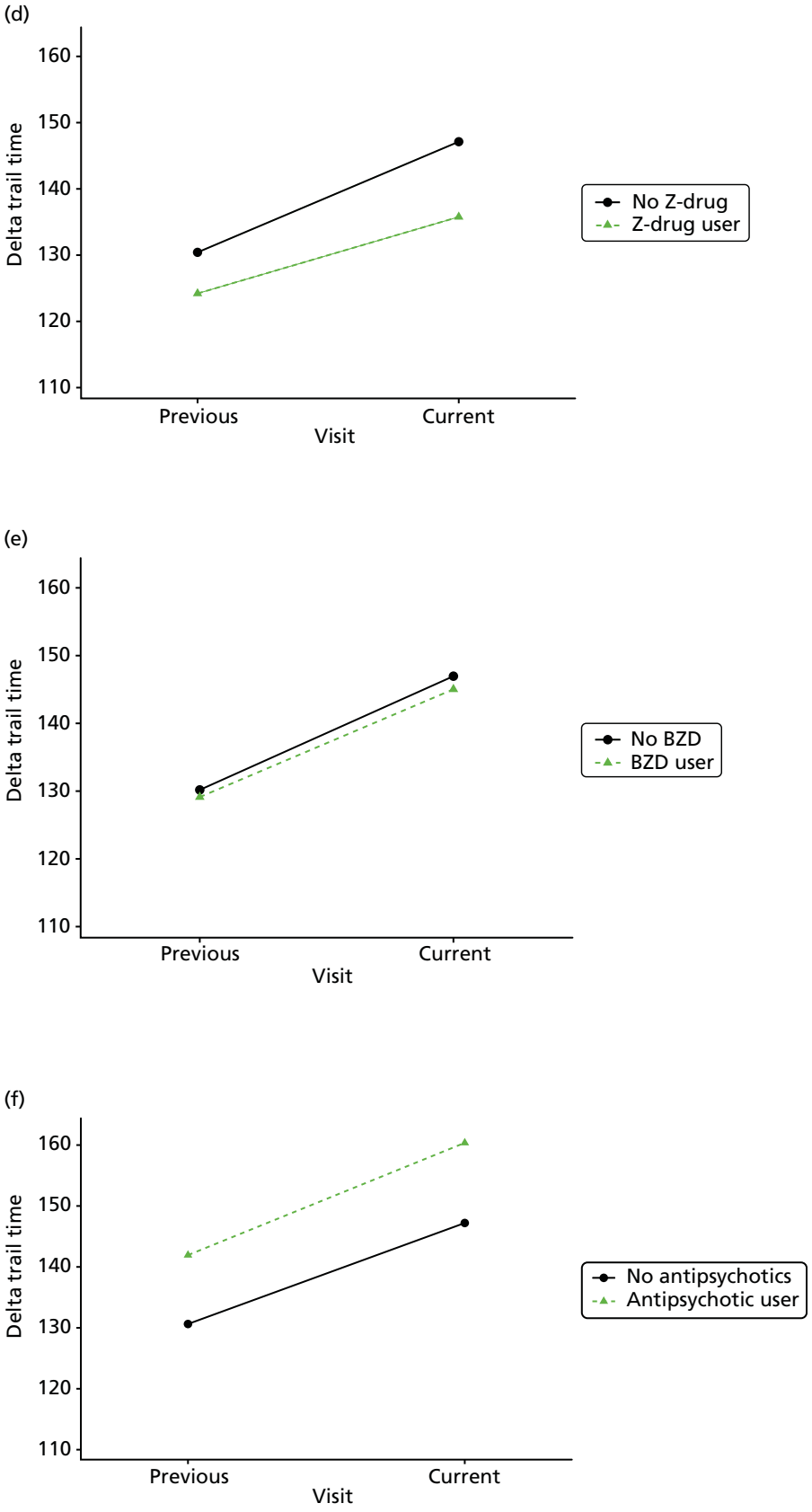

FIGURE 41 Association between changing hypnotic use status between previous and current visit on delta trail time scores (higher scores represent more cognitive impairment) at previous and current visit (a–c). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (d–f). (a) Z-drug; (b) BZD; and (c) antipsychotics. Data from the NACC data set.

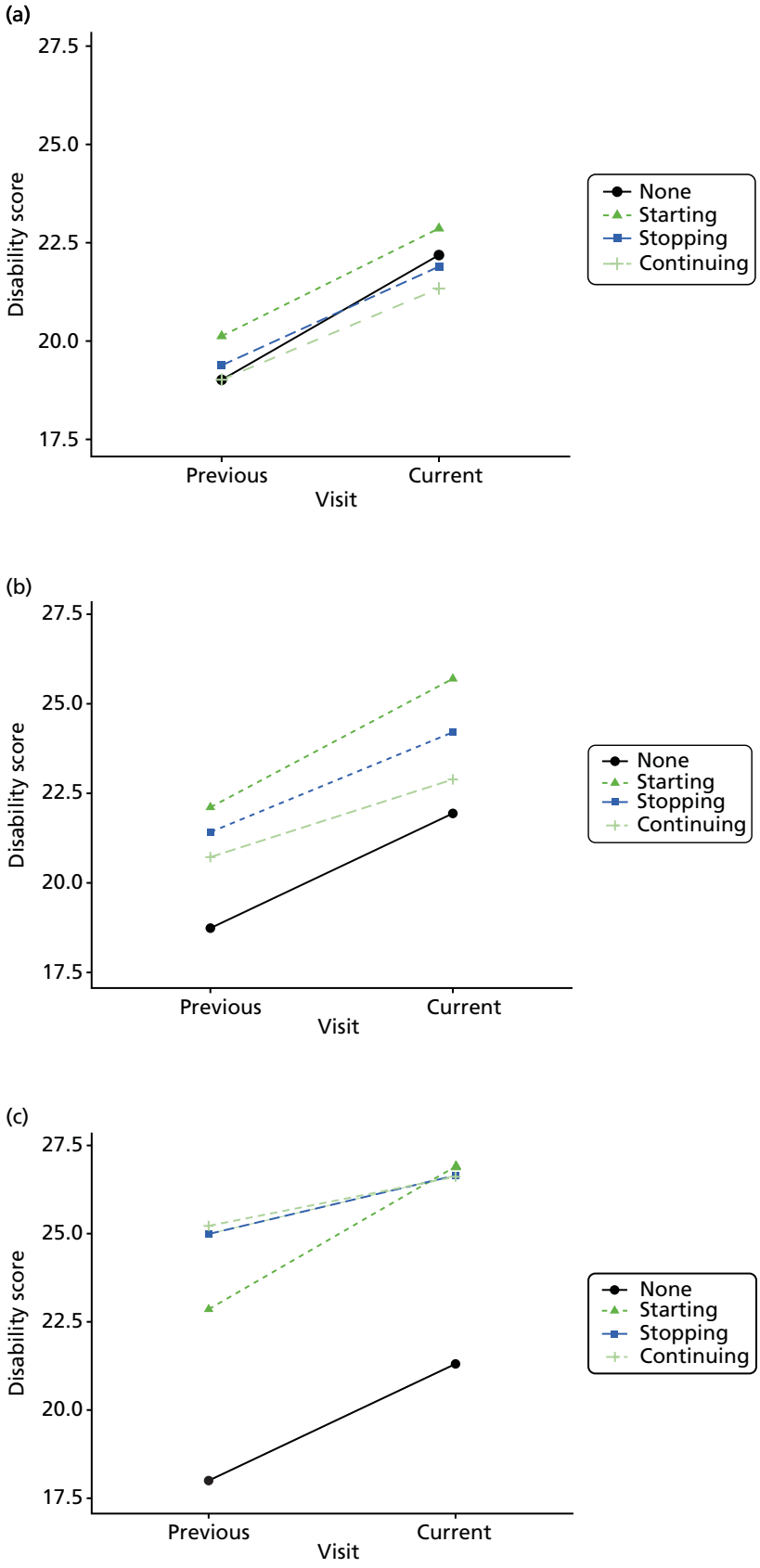

FIGURE 42 Association between changing hypnotic use status between previous and current visit on disability scores (higher scores represent more disability) at previous and current visit (a–c). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (d–f). (a) Z-drug; (b) BZD; and (c) antipsychotics. Data from the NACC data set. (*continued*)

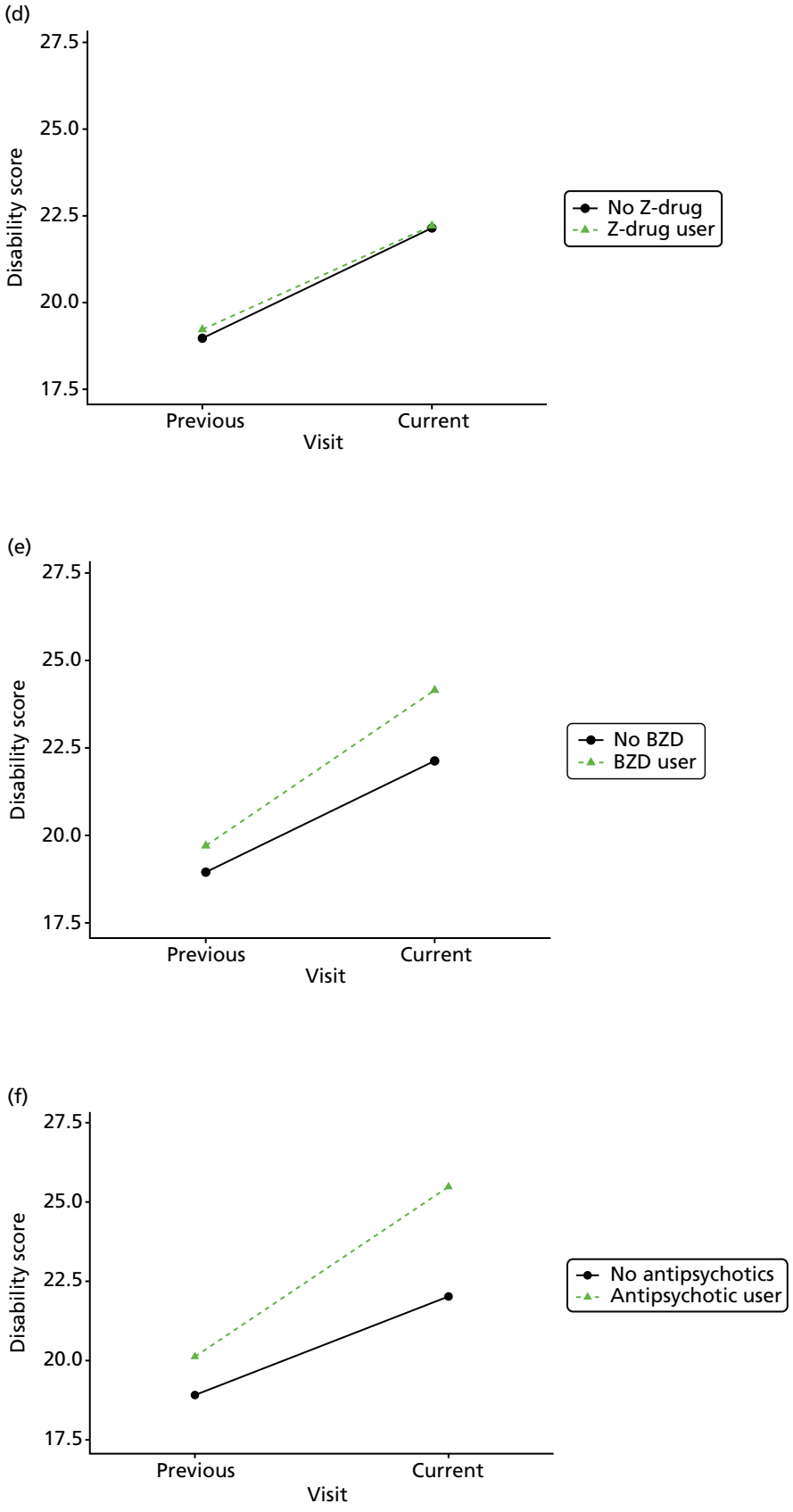

FIGURE 42 Association between changing hypnotic use status between previous and current visit on disability scores (higher scores represent more disability) at previous and current visit (a–c). Mean scores stratified by current hypnotic use, with inverse probability weights used to account for differences in prior predictors of hypnotic use (d–f). (a) Z-drug; (b) BZD; and (c) antipsychotics. Data from the NACC data set.

TABLE 52 Association between hypnotic use and cognitive outcomes, estimated using fixed effects models in specified subgroups of the NACC sample

Subgroup and medication	Outcome, β (95% CI)			
	CDR-SOB	MMSE	Animal naming	Delta trail time
All participants				
Z-drugs	–0.02 (–0.29 to 0.26)	0.02 (–0.54 to 0.59)	–0.15 (–0.58 to 0.29)	2.25 (–7.96 to 12.45)
BZDs	1.01*** (0.86 to 1.15)	–1.43*** (–1.77 to –1.08)	–0.65*** (–0.91 to –0.39)	4.44 (–2.22 to 11.09)
Antipsychotics	1.87*** (1.74 to 1.99)	–1.98*** (–2.27 to –1.69)	–1.19*** (–1.42 to –0.95)	3.00 (–3.64 to 9.64)
New users only				
Z-drugs	–0.30 (–0.86 to 0.27)	0.79 (–0.34 to 1.93)	–0.10 (–0.99 to 0.79)	5.02 (–17.18 to 27.23)
BZDs	1.46*** (1.20 to 1.72)	–1.88*** (–2.52 to –1.24)	–0.58* (–1.09 to –0.07)	–8.75 (–23.25 to 5.75)
Antipsychotics	2.17*** (1.97 to 2.37)	–2.58*** (–3.04 to –2.11)	–1.21*** (–1.58 to –0.84)	–4.14 (–16.02 to 7.74)
Mild/minimal dementia				
Z-drugs	0.04 (–0.29 to 0.37)	0.15 (–0.50 to 0.81)	–0.08 (–0.55 to 0.40)	–0.44 (–11.03 to 10.16)
BZDs	1.11*** (0.94 to 1.28)	–1.55*** (–1.94 to –1.16)	–0.72*** (–1.00 to –0.43)	1.81 (–5.17 to 8.78)
Antipsychotics	2.12*** (1.97 to 2.27)	–2.44*** (–2.78 to –2.09)	–1.27*** (–1.54 to –1.01)	1.78 (–5.21 to 8.78)

*$p < 0.05$, ***$p < 0.001$.

TABLE 53 Association between hypnotic use and neuropsychiatric outcomes, estimated using fixed-effects models in specified subgroups of the NACC sample

Subgroup and medication	Outcome, β (95% CI)			
	Sleep	Agitation	Anxiety	NPI excluding sleep
All participants				
Z-drugs	0.18*** (0.09 to 0.27)	0.08 (–0.003 to 0.17)	0.04 (–0.05 to 0.12)	0.25 (–0.15 to 0.65)
BZDs	0.08*** (0.03 to 0.13)	0.15*** (0.10 to 0.19)	0.11*** (0.06 to 0.15)	0.88*** (0.66 to 1.09)
Antipsychotics	0.10*** (0.06 to 0.14)	0.25*** (0.21 to 0.29)	0.10*** (0.06 to 0.14)	1.28*** (1.10 to 1.46)
New users only				
Z-drugs	0.28** (0.10 to 0.45)	0.31*** (0.14 to 0.48)	0.08 (–0.09 to 0.24)	0.74 (–0.05 to 1.53)
BZDs	0.12** (0.04 to 0.20)	0.22*** (0.15 to 0.30)	0.15*** (0.07 to 0.23)	1.34*** (0.97 to 1.71)
Antipsychotics	0.12*** (0.06 to 0.19)	0.30*** (0.24 to 0.36)	0.07* (0.01 to 0.13)	1.56*** (1.28 to 1.84)
Mild/minimal dementia at baseline				
Z-drugs	0.16** (0.06 to 0.26)	0.04 (–0.05 to 0.14)	0.03 (–0.07 to 0.13)	0.17 (–0.27 to 0.61)
BZDs	0.10*** (0.04 to 0.15)	0.10*** (0.05 to 0.15)	0.10*** (0.05 to 0.15)	0.83*** (0.59 to 1.06)
Antipsychotics	0.12*** (0.08 to 0.17)	0.26*** (0.21 to 0.30)	0.10*** (0.05 to 0.14)	1.36*** (1.16 to 1.57)

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

TABLE 54 Association between hypnotic use, disability and depression, estimated using fixed-effects models in specified subgroups of the NACC sample

Subgroup and medication	Outcome, β (95% CI)	
	Disability	Depression
All participants		
Z-drugs	0.09 (–0.43 to 0.61)	–0.13 (–0.39 to 0.13)
BZDs	0.68*** (0.40 to 0.96)	0.16 (–0.01 to 0.32)
Antipsychotics	1.58*** (1.35 to 1.82)	0.14 (–0.01 to 0.28)
New users only (no Z-drug, BZD or antipsychotic use at baseline)		
Z-drugs	–0.12 (–1.20 to 0.97)	–0.44 (–0.93 to 0.06)
BZDs	0.89*** (0.39 to 1.40)	–0.13 (–0.42 to 0.16)
Antipsychotics	1.37*** (0.98 to 1.75)	0.44*** (0.22 to 0.66)
Mild/minimal dementia at baseline		
Z-drugs	0.17 (–0.44 to 0.79)	–0.07 (–0.35 to 0.20)
BZDs	0.85*** (0.53 to 1.18)	0.13 (–0.04 to 0.30)
Antipsychotics	1.73*** (1.44 to 2.01)	0.18* (0.02 to 0.34)

*$p < 0.05$, ***$p < 0.001$.

Appendix 5 Additional primary care study analyses

Further primary care study results tables, as referred to in the text (*Tables 55–64*).

TABLE 55 Adjusted HRs for adverse events, by sleep disturbance medication relative to Z-drug use

Outcome and sleep drug	Patients (*n*)		Incidence/ 100 PYs	Age, sex adjusted		Fully adjusted[a]	
	Exposed	With outcome		HR	95% CI	HR	95% CI
Fracture							
Z-drug	2997	135	11.3	1.00		1.00	
Low-dose TCA	1913	105	10.2	0.94	0.73 to 1.22	0.91	0.64 to 1.23
BZD	433	20	12.0	1.05	0.66 to 1.68	0.92	0.53 to 1.62
Hip fracture							
Z-drug	2997	66	5.4	1.00		1.00	
Low-dose TCA	1913	56	5.3	1.05	0.73 to 1.51	1.09	0.70 to 1.70
BZD	433	12	7.1	1.30	0.71 to 2.41	1.16	0.51 to 2.65
Forearm fracture							
Z-drug	2997	27	2.2	1.00		1.00	
Low-dose TCA	1913	16	1.5	0.71	0.37 to 1.36	0.89	0.43 to 1.82
BZD	433	< 5	N/A	N/A			
Fall							
Z-drug	2888	399	37.8	1.00		1.00	
Low-dose TCA	1864	286	30.4	0.90	0.77 to 1.05	0.86	0.73 to 1.02
BZD	412	65	43.9	1.16	0.89 to 1.50	1.15	0.87 to 1.54
Mortality							
Z-drug	3089	355	27.8	1.00		1.00	
Low-dose TCA	1942	196	18.1	0.74	0.62 to 0.88	0.75	0.62 to 0.92
BZD	443	66	36.7	1.31	1.00 to 1.73	1.22	0.90 to 1.65
Acute bacterial infection							
Z-drug	2267	408	47.7	1.00		1.00	
Low-dose TCA	1423	273	37.8	0.87	0.75 to 1.02	0.91	0.76 to 1.08
BZD	334	49	38.6	0.81	0.60 to 1.09	0.85	0.62 to 1.17
UTI or acute LRTI							
Z-drug	2267	354	40.2	1.00		1.00	
Low-dose TCA	1423	226	31.3	0.85	0.71 to 1.00	0.89	0.74 to 1.07
BZD	334	41	31.5	0.79	0.57 to 1.10	0.83	0.58 to 1.19
Ischaemic stroke/TIA							
Z-drug	3045	80	6.5	1.00		1.00	
Low-dose TCA	1933	50	4.7	0.77	0.54 to 1.11	0.74	0.49 to 1.12
BZD	438	15	8.7	1.35	0.78 to 2.34	1.50	0.77 to 2.91

continued

TABLE 55 Adjusted HRs for adverse events, by sleep disturbance medication relative to Z-drug use (*continued*)

Outcome and sleep drug	Patients (*n*)		Incidence/ 100 PYs	Age, sex adjusted		Fully adjusted[a]	
	Exposed	With outcome		HR	95% CI	HR	95% CI
Venous thromboembolism							
Z-drug	3074	26	2.1	1.00		1.00	
Low-dose TCA	1940	24	2.2	1.16	0.66 to 2.05	1.02	0.50 to 2.06
BZD	442	< 5	N/A	N/A			
Incident agitation/psychosis							
Z-drug	2574	140	13.6	1.00		1.00	
Low-dose TCA	1633	85	9.7	0.78	0.60 to 1.02	0.84	0.63 to 1.13
BZD	313	36	30.5	2.19	1.53 to 3.13	1.86	1.21 to 2.87

N/A, not applicable; PY, person-year.
a Adjusted for age^2 and the covariates listed in *Table 2* and *Appendix 2, Table 39*, except for forearm fracture, which was also adjusted for eye conditions (ARMD, retinal disorders and glaucoma combined), region as only five categories (South, East, Midlands, North and London), and not adjusted for ethnicity or systolic blood pressure.

TABLE 56 Adjusted HRs for adverse events using different parametrisations of age, by sleep disturbance medication

Outcome and sleep medication	Age parametrisation			
	Restricted cubic splines		Fractional polynomials	
	HR[a]	95% CI	HR[a]	95% CI
Fracture				
No sleep drug	1.00		1.00	
Low-dose TCA	1.12	0.80 to 1.58	1.12	0.80 to 1.58
BZD	1.37	0.70 to 2.66	1.34	0.69 to 2.61
Z-drug	1.42	1.02 to 1.98	1.42	1.02 to 1.97
Hip fracture				
No sleep drug	1.00		1.00	
Low-dose TCA	1.54	0.95 to 2.50	1.54	0.95 to 2.49
BZD	2.10	0.70 to 6.27	2.11	0.72 to 6.12
Z-drug	1.61	1.01 to 2.56	1.60	1.00 to 2.55
Forearm/wrist/hand fracture				
No sleep drug	1.00		1.00	
Low-dose TCA	1.03	0.36 to 2.96	0.99	0.35 to 2.80
Z-drug	1.37	0.58 to 3.25	1.32	0.55 to 3.17
Fall				
No sleep drug	1.00		1.00	
Low-dose TCA	0.84	0.69 to 1.02	0.84	0.69 to 1.02
BZD	1.05	0.75 to 1.48	1.05	0.75 to 1.47
Z-drug	1.05	0.87 to 1.25	1.05	0.87 to 1.25

TABLE 56 Adjusted HRs for adverse events using different parametrisations of age, by sleep disturbance medication (*continued*)

	Age parametrisation			
	Restricted cubic splines		Fractional polynomials	
Outcome and sleep medication	HR[a]	95% CI	HR[a]	95% CI
Mortality				
No sleep drug	1.00		1.00	
Low-dose TCA	0.89	0.72 to 1.11	0.89	0.72 to 1.11
BZD	1.39	0.98 to 1.99	1.38	0.97 to 1.97
Z-drug	1.33	1.09 to 1.63	1.34	1.10 to 1.64
Acute bacterial infection				
No sleep drug	1.00		1.00	
Low-dose TCA	1.00	0.83 to 1.21	1.00	0.83 to 1.21
BZD	0.84	0.59 to 1.21	0.84	0.59 to 1.21
Z-drug	1.09	0.92 to 1.29	1.09	0.92 to 1.29
UTI or acute LRTI				
No sleep drug	1.00		1.00	
Low-dose TCA	0.97	0.79 to 1.19	0.96	0.78 to 1.18
BZD	0.86	0.58 to 1.28	0.85	0.58 to 1.26
Z-drug	1.10	0.92 to 1.32	1.10	0.92 to 1.32
Ischaemic stroke/TIA				
No sleep drug	1.00		1.00	
Low-dose TCA	1.24	0.78 to 1.99	1.21	0.76 to 1.93
BZD	1.56	0.70 to 3.46	1.56	0.69 to 3.52
Z-drug	1.35	0.86 to 2.10	1.33	0.85 to 2.08
Venous thromboembolism				
No sleep drug	1.00		1.00	
Low-dose TCA	1.23	0.56 to 2.69	1.26	0.57 to 2.76
Z-drug	1.71	0.69 to 4.24	1.68	0.70 to 4.05
Incident agitation/psychosis				
No sleep drug	1.00		1.00	
Low-dose TCA	1.43	0.96 to 2.13	1.43	0.96 to 2.13
BZD	5.66	3.13 to 10.26	5.60	3.15 to 9.98
Z-drug	1.72	1.21 to 2.44	1.71	1.21 to 2.42

a Adjusted for the covariates listed in *Table 2* and *Appendix 2, Table 39*, except for forearm fracture, which was also adjusted for eye conditions (ARMD, retinal disorders and glaucoma combined), region as only five categories (South, East, Midlands, North and London), and not adjusted for ethnicity or systolic blood pressure.

TABLE 57 Adjusted HRs for adverse events, according to Z-drug PRN prescription relative to no Z-drug use

Outcome and sleep medication	Patients (*n*)		Age, sex adjusted		Fully adjusted[a]		Test for equality
	Exposed	With outcome	HR	95% CI	HR	95% CI	
Fracture							
No sleep drug	1636	108	1.00		1.00		0.88
Z-drug PRN	488	24	1.62	1.03 to 2.56	1.47	0.86 to 2.50	
Z-drug not PRN	1848	79	1.36	1.00 to 1.86	1.41	0.98 to 2.03	
Hip fracture							
No sleep drug	1636	47	1.00		1.00		0.45
Z-drug PRN	488	13	1.98	1.05 to 3.73	2.18	1.00 to 4.75	
Z-drug not PRN	1848	38	1.48	0.93 to 2.33	1.63	0.96 to 2.77	
Forearm fracture							
No sleep drug	1636	18	1.00		1.00		0.36
Z-drug PRN	488	< 5	1.34	0.39 to 4.63	1.16	0.24 to 5.64	
Z-drug not PRN	1848	22	2.49	1.24 to 4.99	2.42	0.92 to 6.31	
Fall							
No sleep drug	1506	328	1.00		1.00		0.65
Z-drug PRN	461	62	1.19	0.90 to 1.57	1.10	0.82 to 1.48	
Z-drug not PRN	1786	240	1.11	0.94 to 1.33	1.03	0.84 to 1.26	
Mortality							
No sleep drug	1651	266	1.00		1.00		0.57
Z-drug PRN	499	51	1.47	1.21 to 1.79	1.31	1.06 to 1.63	
Z-drug not PRN	1894	184	1.33	1.18 to 1.51	1.24	1.08 to 1.42	
Acute bacterial infection							
No sleep drug	1303	374	1.00		1.00		0.48
Z-drug PRN	354	61	1.23	0.93 to 1.62	1.15	0.85 to 1.56	
Z-drug not PRN	1429	235	1.10	0.92 to 1.30	1.03	0.85 to 1.24	
UTI or acute LRTI							
No sleep drug	1303	328	1.00		1.00		0.45
Z-drug PRN	354	53	1.24	0.92 to 1.66	1.17	0.84 to 1.62	
Z-drug not PRN	1429	199	1.08	0.90 to 1.30	1.03	0.84 to 1.26	
Ischaemic stroke/TIA							
No sleep drug	1640	64	1.00		1.00		0.62
Z-drug PRN	487	12	1.53	0.81 to 2.89	1.76	0.85 to 3.66	
Z-drug not PRN	1877	50	1.48	1.00 to 2.19	1.46	0.86 to 2.46	
Venous thromboembolism							
No sleep drug	1648	22	1.00		1.00		0.58
Z-drug PRN	498	< 5	1.24	0.36 to 4.20	1.44	0.29 to 7.02	
Z-drug not PRN	1889	18	1.69	0.91 to 3.16	2.18	0.81 to 5.85	

TABLE 57 Adjusted HRs for adverse events, according to Z-drug PRN prescription relative to no Z-drug use (*continued*)

Outcome and sleep medication	Patients (*n*)		Age, sex adjusted		Fully adjusted[a]		Test for equality
	Exposed	With outcome	HR	95% CI	HR	95% CI	
Incident agitation/psychosis							
No sleep drug	1282	79	1.00		1.00		0.06
Z-drug PRN	408	13	1.01	0.56 to 1.82	0.92	0.47 to 1.81	
Z-drug not PRN	1576	90	1.69	1.24 to 2.31	1.80	1.23 to 2.63	

a Adjusted for age^2 and the covariates listed in *Table 2* and *Appendix 2, Table 39*, except for forearm fracture, which was also adjusted for eye conditions (ARMD, retinal disorders and glaucoma combined), region as only five categories (South, East, Midlands, North and London), and not adjusted for ethnicity or systolic blood pressure.

TABLE 58 Adjusted HRs for additional medication prescriptions and IRRs for health-care utilisation, by sleep disturbance medication relative to Z-drug use

Outcome and sleep drug	Patients exposed (*n*)	Number of outcomes	Incidence/ 100 PYs	Age, sex adjusted		Fully adjusted[a]	
				HR	95% CI	HR	95% CI
Additional sleep medication							
Z-drug	3089	485	38.0	1.00		1.00	
Low-dose TCA	1942	258	23.8	0.69	0.59 to 0.80	0.65	0.55 to 0.77
BZD	443	45	25.0	0.66	0.48 to 0.89	0.59	0.42 to 0.83
Incident antipsychotic prescription							
Z-drug	2402	355	39.5	1.00		1.00	
Low-dose TCA	1618	164	19.1	0.55	0.46 to 0.67	0.56	0.46 to 0.70
BZD	375	66	59.5	1.25	0.95 to 1.64	1.12	0.84 to 1.51
Incident antidepressant prescription							
Z-drug	2177	236	28.3	1.00		1.00	
BZD	326	31	24.4	0.86	0.59 to 1.26	1.09	0.71 to 1.68
Incident antibiotic prescription							
Z-drug	2430	818	116.4	1.00		1.00	
Low-dose TCA	1552	562	93.8	0.88	0.97 to 1.21	0.87	0.77 to 0.98
BZD	357	116	120.8	1.00	0.82 to 1.23	1.04	0.83 to 1.30
Number of GP visits[b]							
Z-drug	3089	47,259	922.5	1.00		1.00	
Low-dose TCA	1942	33,530	882.1	0.97	0.92 to 1.02	0.91	0.87 to 0.95
BZD	443	6806	791.4	0.91	0.82 to 1.00	0.98	0.90 to 1.06
Number of hospital admissions[b]							
Z-drug	3089	4836	112.3	1.00		1.00	
Low-dose TCA	1942	2991	105.2	0.94	0.85 to 1.03	0.96	0.88 to 1.05
BZD	443	614	98.9	0.88	0.76 to 1.02	0.92	0.79 to 1.06

PY, person-year.
a Adjusted for age^2 and the covariates listed in *Table 2* and *Appendix 2, Table 39*.
b IRRs estimated, not HRs.

TABLE 59 Adjusted HRs for adverse events, by approach towards missing values of BMI and care home status

Outcome and sleep medication	Approach to missing BMI and care home data			
	Missing category		Imputation	
	HR[a]	95% CI	HR[a]	95% CI
Fracture				
No sleep drug	1.00		1.00	
Low-dose TCA	1.12	0.80 to 1.58	1.08	0.77 to 1.52
BZD	1.34	0.69 to 2.61	1.38	0.72 to 2.65
Z-drug	1.40	1.01 to 1.94	1.39	1.00 to 1.93
Hip fracture				
No sleep drug	1.00		1.00	
Low-dose TCA	1.53	0.95 to 2.48	1.46	0.91 to 2.36
BZD	2.07	0.72 to 5.97	1.97	0.68 to 5.67
Z-drug	1.59	1.00 to 2.53	1.56	0.98 to 2.48
Forearm fracture				
No sleep drug	1.00		1.00	
Low-dose TCA	0.99	0.35 to 2.79	0.96	0.34 to 2.73
Z-drug	1.29	0.53 to 3.15	1.29	0.54 to 3.09
Fall				
No sleep drug	1.00		1.00	
Low-dose TCA	0.84	0.69 to 1.02	0.83	0.68 to 1.00
BZD	1.05	0.75 to 1.47	1.04	0.74 to 1.45
Z-drug	1.05	0.87 to 1.25	1.04	0.87 to 1.24
Mortality				
No sleep drug	1.00		1.00	
Low-dose TCA	0.89	0.72 to 1.11	0.92	0.74 to 1.14
BZD	1.38	0.96 to 1.96	1.46	1.04 to 2.05
Z-drug	1.34	1.10 to 1.64	1.35	1.11 to 1.65
Acute bacterial infection				
No sleep drug	1.00		1.00	
Low-dose TCA	1.00	0.83 to 1.21	1.00	0.83 to 1.21
BZD	0.84	0.59 to 1.21	0.86	0.60 to 1.22
Z-drug	1.09	0.92 to 1.29	1.09	0.93 to 1.29
UTI or acute LRTI				
No sleep drug	1.00		1.00	
Low-dose TCA	0.96	0.78 to 1.18	0.96	0.79 to 1.18
BZD	0.85	0.58 to 1.26	0.86	0.58 to 1.27
Z-drug	1.10	0.92 to 1.32	1.10	0.92 to 1.32
Ischaemic stroke/TIA				
No sleep drug	1.00		1.00	
Low-dose TCA	1.20	0.75 to 1.92	1.19	0.74 to 1.91
BZD	1.56	0.69 to 3.51	1.54	0.67 to 3.54
Z-drug	1.33	0.85 to 2.07	1.33	0.85 to 2.08

TABLE 59 Adjusted HRs for adverse events, by approach towards missing values of BMI and care home status (*continued*)

	Approach to missing BMI and care home data			
	Missing category		Imputation	
Outcome and sleep medication	HR[a]	95% CI	HR[a]	95% CI
Venous thromboembolism				
No sleep drug	1.00		1.00	
Low-dose TCA	1.23	0.56 to 2.69	1.27	0.59 to 2.72
Z-drug	1.66	0.69 to 3.98	1.67	0.67 to 4.13
Incident agitation/psychosis				
No sleep drug	1.00		1.00	
Low-dose TCA	1.43	0.96 to 2.13	1.39	0.93 to 2.06
BZD	5.61	3.14 to 10.01	5.38	2.99 to 9.68
Z-drug	1.71	1.21 to 2.42	1.71	1.22 to 2.42

a Adjusted for age[2] and the covariates listed in *Table 2* and *Appendix 2, Table 39*, except for forearm fracture, which was also adjusted for eye conditions (ARMD, retinal disorders and glaucoma combined), region as only five categories (South, East, Midlands, North and London), and not adjusted for ethnicity or systolic blood pressure.

TABLE 60 Adjusted HRs for additional medication prescriptions and IRRs for health-care utilisation, by approach towards missing values of BMI and care home status

	Approach to missing BMI and care home data			
	Missing category		Imputation	
Outcome and sleep drug	HR[a]	95% CI	HR[a]	95% CI
Additional sleep medication				
No sleep drug	1.00		1.00	
Low-dose TCA	0.79	0.65 to 0.97	0.79	0.65 to 0.96
BZD	0.63	0.43 to 0.93	0.63	0.43 to 0.92
Z-drug	1.13	0.95 to 1.35	1.14	0.95 to 1.36
Incident antipsychotic prescription				
No sleep drug	1.00		1.00	
Low-dose TCA	1.17	0.90 to 1.53	1.17	0.90 to 1.53
BZD	2.23	1.50 to 3.32	2.19	1.47 to 3.27
Z-drug	2.01	1.60 to 2.52	2.00	1.59 to 2.51
Incident antidepressant prescription				
No sleep drug	1.00		1.00	
BZD	1.77	1.02 to 3.09	1.73	1.00 to 2.98
Z-drug	2.05	1.56 to 2.68	2.05	1.56 to 2.68

continued

TABLE 60 Adjusted HRs for additional medication prescriptions and IRRs for health-care utilisation, by approach towards missing values of BMI and care home status (*continued*)

	Approach to missing BMI and care home data			
	Missing category		Imputation	
Outcome and sleep drug	HR[a]	95% CI	HR[a]	95% CI
Incident antibiotic prescription				
No sleep drug	1.00		1.00	
Low-dose TCA	1.13	0.99 to 1.29	1.14	0.99 to 1.30
BZD	1.35	1.06 to 1.71	1.36	1.07 to 1.72
Z-drug	1.26	1.12 to 1.42	1.26	1.12 to 1.43
Number of GP visits[b]				
No sleep drug	1.00		1.00	
Low-dose TCA	1.01	0.96 to 1.07	1.01	0.96 to 1.07
BZD	1.05	0.97 to 1.14	1.05	0.97 to 1.14
Z-drug	1.14	1.08 to 1.19	1.14	1.09 to 1.20
Number of hospital admissions[b]				
No sleep drug	1.00		1.00	
Low-dose TCA	1.04	0.95 to 1.15	1.03	0.94 to 1.14
BZD	0.97	0.84 to 1.13	0.95	0.82 to 1.11
Z-drug	1.12	1.03 to 1.21	1.11	1.02 to 1.21

a Adjusted for age^2 and the covariates listed in *Table 2* and *Appendix 2, Table 39*.
b IRRs estimated, not HRs.

TABLE 61 Adjusted HRs for adverse events, by sleep disturbance medication relative to no medication in patients diagnosed with sleep disturbance (excluding mention of a satisfactory sleep pattern)

	Age, sex adjusted		Fully adjusted[a]	
Outcome and sleep medication	HR	95% CI	HR	95% CI
Fracture				
No sleep drug	1.00		1.00	
Low-dose TCA	1.22	0.88 to 1.70	1.00	0.66 to 1.52
BZD	1.31	0.76 to 2.26	1.62	0.70 to 3.75
Z-drug	1.32	0.95 to 1.84	1.34	0.90 to 1.99
Hip fracture				
No sleep drug	1.00		1.00	
Low-dose TCA	1.35	0.85 to 2.14	1.17	0.64 to 2.14
Z-drug	1.28	0.81 to 2.02	1.33	0.77 to 2.32
Forearm/wrist/hand fracture				
No sleep drug	1.00		1.00	
Low-dose TCA	0.86	0.39 to 1.89	0.94	0.30 to 2.90
Z-drug	1.45	0.65 to 3.23	1.24	0.43 to 3.60

TABLE 61 Adjusted HRs for adverse events, by sleep disturbance medication relative to no medication in patients diagnosed with sleep disturbance (excluding mention of a satisfactory sleep pattern) (*continued*)

	Age, sex adjusted		Fully adjusted[a]	
Outcome and sleep medication	HR	95% CI	HR	95% CI
Fall				
No sleep drug	1.00		1.00	
Low-dose TCA	0.83	0.69 to 1.00	0.72	0.58 to 0.90
BZD	1.06	0.79 to 1.44	0.88	0.60 to 1.30
Z-drug	0.90	0.75 to 1.07	0.87	0.71 to 1.07
Mortality				
No sleep drug	1.00		1.00	
Low-dose TCA	0.87	0.70 to 1.08	0.78	0.61 to 1.01
BZD	1.51	1.09 to 2.08	0.98	0.64 to 1.52
Z-drug	1.23	1.00 to 1.51	1.09	0.86 to 1.38
Acute bacterial infection				
No sleep drug	1.00		1.00	
Low-dose TCA	0.91	0.76 to 1.10	0.92	0.74 to 1.15
BZD	0.78	0.56 to 1.10	0.68	0.43 to 1.06
Z-drug	1.06	0.89 to 1.27	0.98	0.80 to 1.19
UTI or acute LRTI				
No sleep drug	1.00		1.00	
Low-dose TCA	0.86	0.70 to 1.05	0.86	0.68 to 1.09
BZD	0.82	0.57 to 1.17	0.76	0.46 to 1.23
Z-drug	1.04	0.86 to 1.26	0.97	0.79 to 1.19
Ischaemic stroke/TIA				
No sleep drug	1.00		1.00	
Low-dose TCA	0.99	0.63 to 1.56	1.11	0.64 to 1.93
BZD	1.66	0.84 to 3.28	1.38	0.22 to 8.71
Z-drug	1.42	0.91 to 2.22	1.17	0.68 to 2.03
Venous thromboembolism				
No sleep drug	1.00		1.00	
Low-dose TCA	1.16	0.62 to 2.18	0.93	0.39 to 2.17
Z-drug	1.16	0.60 to 2.22	1.37	0.61 to 3.10
Incident agitation/psychosis				
No sleep drug	1.00		1.00	
Low-dose TCA	0.89	0.63 to 1.26	1.04	0.68 to 1.58
BZD	2.64	1.65 to 4.21	4.11	2.15 to 7.84
Z-drug	1.06	0.77 to 1.45	1.10	0.77 to 1.56

a Adjusted for age^2 and the covariates listed in *Table 2* and *Appendix 2*, *Table 39*, except for hip fracture and forearm fracture outcomes, which were also adjusted for eye conditions (ARMD, retinal disorders and glaucoma combined), region as only five categories (South, East, Midlands, North and London), and not adjusted for ethnicity or systolic blood pressure; and for ischaemic stroke/TIA and venous thromboembolism outcomes, which were also adjusted for eye conditions (ARMD, retinal disorders and glaucoma combined), and not adjusted for region, ethnicity, systolic blood pressure or BMI.

TABLE 62 Adjusted HRs for additional medication prescriptions and IRRs for health-care utilisation, by sleep disturbance medication relative to patients diagnosed with sleep disturbance (excluding mention of satisfactory sleep pattern)

	Age, sex adjusted		Fully adjusted[a]	
Outcome and sleep drug	HR	95% CI	HR	95% CI
Additional sleep medication				
No sleep drug	1.00		1.00	
Low-dose TCA	0.58	0.48 to 0.69	0.56	0.46 to 0.69
BZD	0.50	0.36 to 0.70	0.45	0.30 to 0.66
Z-drug	0.82	0.70 to 0.96	0.80	0.67 to 0.96
Incident antipsychotic prescription				
No sleep drug	1.00		1.00	
Low-dose TCA	0.76	0.60 to 0.98	0.75	0.57 to 1.00
BZD	1.45	1.04 to 2.03	1.16	0.76 to 1.79
Z-drug	1.39	1.11 to 1.74	1.34	1.05 to 1.73
Incident antidepressant prescription				
No sleep drug	1.00		1.00	
BZD	1.33	0.86 to 2.05	1.47	0.74 to 2.92
Z-drug	1.47	1.12 to 1.93	1.69	1.25 to 2.30
Incident antibiotic prescription				
No sleep drug	1.00		1.00	
Low-dose TCA	1.02	0.89 to 1.17	1.02	0.87 to 1.19
BZD	1.20	0.96 to 1.52	1.29	0.99 to 1.70
Z-drug	1.17	1.03 to 1.34	1.13	0.98 to 1.30
Number of GP visits[b]				
No sleep drug	1.00		1.00	
Low-dose TCA	1.09	1.01 to 1.17	0.98	0.92 to 1.04
BZD	1.05	0.94 to 1.16	1.01	0.92 to 1.11
Z-drug	1.14	1.06 to 1.21	1.09	1.03 to 1.15
Number of hospital admissions[b]				
No sleep drug	1.00		1.00	
Low-dose TCA	1.00	0.90 to 1.12	0.97	0.87 to 1.08
BZD	0.91	0.79 to 1.06	0.91	0.78 to 1.07
Z-drug	1.07	0.97 to 1.18	1.04	0.95 to 1.14

a Adjusted for age[2] and the covariates listed in *Table 2* and *Appendix 2, Table 39*.
b IRRs estimated, not HRs.

TABLE 63 Adjusted HRs for adverse events recorded in CPRD only, by sleep disturbance medication

Outcome and sleep medication	Patients with outcome in CPRD (*n*)	Per cent of main analysis outcomes	Age, sex adjusted		Fully adjusted[a]	
			HR	95% CI	HR	95% CI
Fracture						
No sleep drug	83	77	1.00		1.00	
Low-dose TCA	76	72	1.25	0.91 to 1.73	1.07	0.72 to 1.60
BZD	13	65	1.21	0.68 to 2.18	1.05	0.44 to 2.51
Z-drug	90	67	1.23	0.89 to 1.68	1.27	0.87 to 1.87
Hip fracture						
No sleep drug	35	74	1.00		1.00	
Low-dose TCA	37	66	1.46	0.91 to 2.35	1.38	0.78 to 2.44
BZD	7	58	1.71	0.74 to 3.94	2.35	0.54 to 10.11
Z-drug	40	61	1.38	0.85 to 2.23	1.38	0.75 to 2.52
Forearm fracture						
No sleep drug	13	72	1.00		1.00	
Low-dose TCA	11	69	1.04	0.45 to 2.41	0.87	0.22 to 3.51
Z-drug	20	74	1.82	0.82 to 4.07	1.63	0.56 to 4.75
Fall						
No sleep drug	245	75	1.00		1.00	
Low-dose TCA	183	64	0.84	0.70 to 1.03	0.77	0.61 to 0.96
BZD	46	71	1.26	0.91 to 1.74	1.09	0.74 to 1.62
Z-drug	269	67	1.01	0.84 to 1.21	1.03	0.83 to 1.27
Acute bacterial infection						
No sleep drug	239	64	1.00		1.00	
Low-dose TCA	165	60	0.97	0.79 to 1.19	0.99	0.77 to 1.27
BZD	37	76	1.11	0.78 to 1.58	1.01	0.67 to 1.54
Z-drug	243	60	1.13	0.93 to 1.36	1.14	0.91 to 1.42
UTI or acute LRTI						
No sleep drug	206	63	1.00		1.00	
Low-dose TCA	127	56	0.86	0.69 to 1.07	0.90	0.69 to 1.17
BZD	30	73	1.07	0.73 to 1.58	1.00	0.63 to 1.60
Z-drug	184	52	0.98	0.80 to 1.21	1.01	0.79 to 1.28
Ischaemic stroke/TIA						
No sleep drug	47	73	1.00		1.00	
Low-dose TCA	37	74	1.02	0.66 to 1.58	1.17	0.67 to 2.06
BZD	12	80	1.92	0.98 to 3.74	2.88	1.10 to 7.52
Z-drug	52	65	1.21	0.79 to 1.85	1.22	0.72 to 2.08
Venous thromboembolism						
No sleep drug	14	64	1.00		1.00	
Low-dose TCA	12	50	1.32	0.61 to 2.86	1.12	0.29 to 4.34
Z-drug	14	54	1.18	0.56 to 2.49	1.06	0.36 to 3.12

continued

TABLE 63 Adjusted HRs for adverse events recorded in CPRD only, by sleep disturbance medication (*continued*)

Outcome and sleep medication	Patients with outcome in CPRD (*n*)	Per cent of main analysis outcomes	Age, sex adjusted		Fully adjusted[a]	
			HR	95% CI	HR	95% CI
Incident agitation/psychosis						
No sleep drug	74	94	1.00		1.00	
Low-dose TCA	77	91	1.30	0.93 to 1.81	1.51	1.01 to 2.27
BZD	34	94	3.88	2.50 to 6.02	5.76	3.22 to 10.28
Z-drug	126	90	1.53	1.14 to 2.06	1.77	1.24 to 2.54

a Adjusted for age^2 and the covariates listed in *Table 2* and *Appendix 2, Table 39*, except for forearm fracture and venous thromboembolism, which were also adjusted for eye conditions (ARMD, retinal disorders and glaucoma combined) and not adjusted for region, ethnicity or systolic blood pressure.

TABLE 64 Adjusted HRs for adverse events, for patients initiating Z-drugs compared with patients discontinuing Z-drugs

Outcome and sleep drug	Patients (*n*)		Incidence/ 100 PYs	Age, sex adjusted		Fully adjusted[a]	
	Exposed	With outcome		HR	95% CI	HR	95% CI
Fracture							
Discontinued Z-drug	1265	80	8.2	1.00		1.00	
New Z-drug	2997	135	11.3	1.24	0.94 to 1.65	1.31	0.94 to 1.84
Hip fracture							
Discontinued Z-drug	1265	45	4.5	1.00		1.00	
New Z-drug	2997	66	5.4	1.13	0.77 to 1.65	1.01	0.63 to 1.62
Forearm fracture							
Discontinued Z-drug	1265	17	1.7	1.00		1.00	
New Z-drug	2997	27	2.2	1.24	0.65 to 2.39	1.60	0.75 to 3.41
Fall							
Discontinued Z-drug	1236	221	25.7	1.00		1.00	
New Z-drug	2888	399	37.8	1.25	1.06 to 1.47	1.30	1.06 to 1.58
Mortality							
Discontinued Z-drug	1274	182	17.8	1.00		1.00	
New Z-drug	3089	355	27.8	1.47	1.23 to 1.77	1.45	1.17 to 1.81
Acute bacterial infection							
Discontinued Z-drug	1029	251	35.5	1.00		1.00	
New Z-drug	2267	408	47.7	1.21	1.03 to 1.42	1.34	1.11 to 1.63
UTI or acute LRTI							
Discontinued Z-drug	1029	211	28.9	1.00		1.00	
New Z-drug	2267	354	40.0	1.24	1.04 to 1.48	1.38	1.12 to 1.70
Ischaemic stroke/TIA							
Discontinued Z-drug	1268	43	4.3	1.00		1.00	
New Z-drug	3045	80	6.5	1.44	0.97 to 2.12	1.23	0.76 to 1.97

TABLE 64 Adjusted HRs for adverse events, for patients initiating Z-drugs compared with patients discontinuing Z-drugs (*continued*)

Outcome and sleep drug	Patients (*n*)		Incidence/ 100 PYs	Age, sex adjusted		Fully adjusted[a]	
	Exposed	With outcome		HR	95% CI	HR	95% CI
Venous thromboembolism							
Discontinued Z-drug	1273	12	1.2	1.00		1.00	
New Z-drug	3074	26	2.1	1.68	0.83 to 3.41	2.71	0.88 to 8.31
Incident agitation/psychosis							
Discontinued Z-drug	1039	41	4.9	1.00		1.00	
New Z-drug	2574	140	13.6	2.26	1.60 to 3.19	2.16	1.47 to 3.17
Incident antipsychotic prescription							
Discontinued Z-drug	1274	107	13.8	1.00		1.00	
New Z-drug	2402	355	39.5	2.09	1.59 to 2.75	2.66	2.09 to 3.40
Incident antidepressant prescription							
Discontinued Z-drug	825	66	10.6	1.00		1.00	
New Z-drug	2177	236	28.3	2.09	1.59 to 2.75	2.20	1.62 to 2.99
Incident antibiotic prescription							
Discontinued Z-drug	1087	483	88.8	1.00		1.00	
New Z-drug	2430	818	116.4	1.14	1.02 to 1.27	1.21	1.07 to 1.37

PY, person-year.

a Adjusted for age[2] and the covariates listed in *Table 2* and *Appendix 2, Table 39*, except for forearm fracture, which was also adjusted for eye conditions (ARMD, retinal disorders and glaucoma combined) and not adjusted for region, ethnicity or systolic blood pressure.

Appendix 6 Additional WHELD trial analyses

TABLE 65 Adjusted additional change in QUALID, NPI-NH and NPI-NH sleep scores, by pattern of Z-drug use

	Z-drug				
Scale	Pattern	*n*	Mean change (SD)	Beta (95% CI)	Beta[a] (95% CI)
NPI-NH excluding sleep	None	514	0.44 (16.06)	0.00	0.00
	Stopping	26	0.65 (17.02)	0.22 (–6.34 to 6.77)	1.46 (–5.49 to 8.40)
	Starting	25	–1.84 (20.44)	–2.28 (–8.96 to 4.40)	–2.52 (–10.07 to 5.03)
	Continuing	62	–1.40 (19.12)	–1.84 (–6.23 to 2.55)	0.09 (–4.51 to 4.69)
NPI-NH sleep	None	514	0.10 (0.59)	0.00	0.00
	Stopping	26	0.27 (0.53)	0.17 (–0.07 to 0.41)	0.11 (–0.14 to 0.37)
	Starting	25	0.16 (0.62)	0.06 (–0.18 to 0.30)	0.05 (–0.23 to 0.33)
	Continuing	62	0.11 (0.70)	0.01 (–0.15 to 0.17)	0.07 (–0.10 to 0.24)
QUALID	None	502	0.22 (7.34)	0.00	0.00
	Stopping	26	1.88 (6.26)	1.66 (–1.37 to 4.70)	2.28 (–0.79 to 5.34)
	Starting	23	–0.17 (9.16)	–0.40 (–3.61 to 2.82)	–0.33 (–3.79 to 3.13)
	Continuing	59	–0.09 (10.07)	–0.31 (–2.38 to 1.77)	0.86 (–1.23 to 2.95)

a Adjusted for age, sex, ethnicity, marital status, baseline CDR, Abbey Pain Scale score, comorbidity and changes in co-medication use. Change in QUALID scores also adjusted for baseline sleep disturbance (a NPI-NH sleep score > 0).

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