

## **Prevalence of Frailty in Mild to Moderate Alzheimer's Disease: A Systematic Review and Meta-analysis**

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## **ABSTRACT**

**Background:** Frailty is a state of increased vulnerability to poor resolution of homeostasis as a consequence of age-related decreased physiological reserves. Although physical frailty and cognitive impairment have been shown to be associated, evidence on the prevalence of frailty in Alzheimer's disease is scarce.

**Objective:** To conduct a systematic review on the prevalence of frailty and to combine the data to synthesize the pooled prevalence of physical frailty among patients with Alzheimer's disease.

**Method:** Five electronic databases (Embase, MEDLINE, CINAHL Plus, PsycINFO, and the Cochrane Library) were searched for studies providing cross-sectional data on physical frailty among patients with Alzheimer's disease published from 2000 to January 2016.

**Results:** Of 2,564 studies identified through the systematic review, five studies incorporating 534 patients with Alzheimer's disease were included for the meta-analysis. The prevalence of frailty varied with a wide range from 11.1% to 50.0% and the pooled prevalence was 31.9% (five studies, 95% confidence interval (CI)=15.7%-48.5%). The high degree of heterogeneity was observed in all analyses. A borderline publication bias was detected.

**Conclusion:** The current study showed that frailty is highly prevalent in older patients with Alzheimer's disease in the community with the pooled prevalence of 31.9%. The true prevalence may be much higher given that end-stage patients may not be included. This information is important for clinicians and researchers.

## INTRODUCTION

Frailty is defined as a state of increased vulnerability and poor resolution of homeostasis after a stressor event as a consequence of age-related decreased physiological reserves.[1] Frail individuals are at increased risk of falls, disability, hospitalization, institutionalization, fracture, a poor quality of life, and death.[1-7] Despite an increasing amount of evidence on frailty in the literature, there has been no international consensus on how best to operationalize frailty.[8] The most popular criteria to operationalize frailty is the so-called frailty phenotype proposed by Fried et al. using the Cardiovascular Health Study (CHS).[9] In this operationalization, frailty is characterized by only physical components, including unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity.[9]

Although the CHS criteria remain the most frequently used,[10] there has been considerable debate on whether, in addition to physical components, other features, such as cognitive, psychological, and social factors, should be included in the conceptualization of frailty to capture the heterogeneous elderly population more holistically and identify at-risk individuals more precisely.[8] Multiple studies have shown cross-sectional and prospective associations of frailty with cognitive impairment and dementia.[11; 12] In one cross-sectional study of Japanese community-dwelling older people, those with both physical frailty and cognitive impairment had the highest disability risks in most instrumental activities of daily living (IADL) compared with those with either, one or none of these factors.[13] Another longitudinal study using the Three-City Study cohort showed that adding cognitive impairment to physical frailty improved the predictive abilities for incident disability, hospitalization, and mortality.[14] Therefore, cognition has increasingly been recognized as a component of frailty,[8; 15] and some of the multidimensional frailty criteria have already included cognitive impairment.[16] Furthermore, there is an emerging new concept, “cognitive frailty”, which was first proposed by an international consensus group organized by the International Academy on Nutrition and Aging and the International Association of Gerontology and Geriatrics, as a clinical manifestation characterized by the co-existence of physical frailty and cognitive impairment without dementia.[17]

In a previous systematic review, the overall weighted prevalence of frailty was reported to be 10.7% with a considerably wide range from 4.0% to 59.1% in older people over 65 years old in the community.[18] The prevalence increases as people age, and up to one-fourth of people aged 85 years and older are frail.[18; 19] Frailty has been predominantly studied in general elderly populations, and selected populations, such as patients with dementia, are relatively understudied with scarce evidence in the literature. Therefore, the overall prevalence of frailty among this highly heterogeneous dementia population is unknown. Although one could argue that all patients with dementia could be classified as being frail or pre-frail if cognitive impairment was a frailty component, it is also evident that some patients with dementia remain physically fit even when severely impaired cognitively. Dementia is defined as loss of memory and one other cognitive function, sufficient to cause impairment in everyday functioning, and is therefore by definition a cause of disability but not necessarily of frailty. Conversely, physical frailty was shown to be a significant predictor of newly developing dementia in a recent systematic review and meta-analysis.[12]

Given that we expect an increasing number of patients with dementia as the world population ages,[20] estimating the overall prevalence of frailty among older people with Alzheimer’s disease, which is the most common cause of dementia,[21] is of great importance. The aims of this study were two-fold: (1) to conduct a systematic search of the literature on the frailty

status of community-dwelling older people with Alzheimer's disease and (2) to combine the data on prevalence of frailty to synthesize the pooled estimates.

## **METHOD**

### **Data Sources and Search Strategy**

A systematic literature search was conducted in January 2016 based on a protocol developed according to Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA)[22] and Meta-analysis of Observational Studies in Epidemiology (MOOSE)[23] statements. The protocol has been registered at PROSPERO website.[24] Five electronic databases (Embase, MEDLINE, CINAHL Plus, PsycINFO, and the Cochrane Library) were searched for studies published in 2000 or later with an explosion function if available and without language restriction. A combination of Medical Subject Headings (MeSH) and text words were used as:

(Dementia (MeSH)) OR (Alzheimer('s) Disease (MeSH)) OR (Dementia with Lewy Bodies (MeSH)) OR (Lewy Body Disease (MeSH)) OR (Multiinfarct Dementia (MeSH)) OR (Dementia, Multi-Infarct (MeSH)) OR (Vascular Dementia (MeSH)) OR (Dementia, Vascular (MeSH)) OR (Frontotemporal Dementia (MeSH)) OR (Frontal Variant Frontotemporal Dementia (MeSH)) OR (Dementia, Senile (MeSH)) OR (Senile Dementia (MeSH)) OR (Presenile Dementia (MeSH)) OR (Dementia, Presenile (MeSH)) OR (Delirium, Dementia, Amnestic, Cognitive Disorders (MeSH)) OR (dementia) OR (alzheimer)

AND

(Frail Elderly (MeSH)) OR (Frailty Syndrome (MeSH)) OR (Frailty).

Relevant studies and related review articles were used for additional studies; their bibliographies were reviewed and studies displayed as "Similar articles" by PubMed when the relevant studies were searched were also examined.

### **Study Selection**

Studies were considered potentially eligible and included if they (1) included patients with Alzheimer's disease based on established diagnostic criteria, such as the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria or the Diagnostic and Statistical Manual of Mental Disorders in the community with a mean age of 65 years and older, (2) used a cross-sectional design or observational design with baseline data, (3) provided prevalence of frailty and/or pre-frailty or sufficient data to calculate prevalence of frailty, and (4) defined and categorized frailty by validated criteria based on physical components, such as CHS criteria, the Study of Osteoporotic Fractures (SOF) criteria or their modified versions. Studies were excluded if they (1) used population without Alzheimer's disease or did not provide data only on individuals with Alzheimer's disease, (2) did not use validated frailty criteria or used continuous index to describe frailty, such as the Frailty Index (FI) and did not categorize frailty status, or (3) were a randomized controlled trial, review article, editorial, comment, or personal opinion. Mild cognitive impairment was not considered in this study. If multiple studies used the same cohort, the one with the largest sample size was included. Two researchers (GK and AL) independently screened the titles, abstracts, and full-texts of the studies identified by the systematic literature search for eligibility. Disagreements were solved by discussion.

### **Data Extraction**

The data extracted from the included studies were first author, study cohort name, publication year, location, sample size and description, age (mean and range or age criterion for inclusion), proportion of female participants, frailty criteria, diagnostic criteria, and numbers

and percentages of frail, pre-frail, and robust participants. Authors of the potentially eligible studies were contacted for additional data.

### **Methodological Quality Assessment**

Methodological quality of all eligible studies was examined using the six criteria from a tool for critically assessing studies on prevalence or incidence as an outcome.[25] Studies were considered to have adequate quality in terms of methodology if the studies meet three of more criteria.

### **Statistical Analysis**

Numbers of the entire cohort and those who were classified as being robust (or non-frail), pre-frail, and frail were extracted directly from the studies or attempts were made to obtain data by contacting the authors. Heterogeneity across the studies was assessed using a chi-square test and was considered to be present if  $p < 0.05$ . The degree of the heterogeneity was assessed using  $I^2$  statistic. The heterogeneity was considered as high, moderate, and low when  $I^2$  values were 75%, 50%, and 25%, respectively.[26] Pooled prevalence of being robust, pre-frail, and frail along with 95% confidence intervals (CI) were calculated using a random-effects model if heterogeneity was present and using a fixed-effects model if heterogeneity was absent. Begg-Mazumdar's and Egger's tests were used for possible publication bias. All statistical analyses were conducted using StatsDirect (ver. 2.8, StatsDirect, Cheshire, UK). Statistical significance was set at  $p$  value of less than 0.05.

## **RESULTS**

### **Selection Process**

The systematic search of the literature using the five electronic databases yielded 2,564 citations, and two additional studies were identified from other relevant studies. From the 2,566 studies, 832 duplicate studies and 1,713 studies that were considered to be not relevant were excluded, leaving 21 studies for full-text review. Nine studies were excluded for being editorial, review, comment, or poster abstracts; three for using the same cohorts; and two each for not categorizing frailty status and not showing data of interest. The five studies remaining were considered to have adequate methodological quality and were included in a meta-analysis (**Tables 1 and 2**). **Figure 1** shows a flowchart of the study selection.

### **Study Characteristics**

The study characteristics of all the included studies[27-31] are summarized in **Table 1**. All studies were published only recently between 2012 and 2016. Study locations were Italy,[27; 30] Singapore,[31] Finland,[28] and the Netherlands.[29] The smallest and largest sample sizes were 38[30] and 207.[29] Two types of data were found: data of patients with Alzheimer's disease from a large population-based study[28; 30] and data of participants recruited from a specialty healthcare service (e.g. memory clinic).[27; 29; 31] The diagnostic criteria used were NINCDS-ADRDA criteria[29-31] or the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DMS-IV).[27; 28] The mean age ranged from 73.1[30] to 82.8[27] years. The proportion of female participants was from 45.2%[30] to 77.1%.[27] Modified versions of CHS and SOF criteria were used by four studies[28-31] and one study,[27] respectively. Three studies used three frailty categories (robust, pre-frail, and frail),[27-29] while two used dichotomized categories (non-frail and frail).[30; 31] Both Begg-Mazumdar's and Egger's tests detected a borderline publication bias.

### **Prevalence of Frailty**

The prevalence of frailty varied widely from study to study with a range from 11.1%[29] to 50.0%[30] and its pooled prevalence was 31.9% (five studies, 95%CI=15.7%-48.5%). Among these, three studies[27-29] provided three frailty categories (frailty, pre-frailty, and robustness), which were used to calculate pooled prevalence of pre-frailty and robustness, and two studies[30; 31] provided two frailty categories (frailty and robustness). The pooled prevalence of pre-frailty and robustness was 41.4% (three studies, 95%CI=28.3%-55.2%) and 29.0% (three studies, 95%CI=18.4%-40.9%), respectively. The pooled prevalence of frailty recalculated using the three studies providing three frailty categories was 28.5% (three studies, 95%CI=8.6%-54.3%, data not shown in Figure) The random-effects models were used for these pooled analyses due to the high degree of heterogeneity observed ( $I^2$  value=84.2%-96.5%). (Figure 2)

## DISCUSSION

This systematic review and meta-analysis study identified five studies including 534 patients with Alzheimer's disease with probable mild to moderate severity and showed that the pooled estimate of frailty prevalence was 31.9%. Although frailty was, as expected, more prevalent in patients with Alzheimer's disease than in the general elderly population in the community,[18; 32] the prevalence rate appears comparable with or lower than those of other selected populations. For instance, previous systematic reviews have showed a median prevalence of 32% (range 11%-78%) in cancer patients,[33] pooled prevalence of 36.8% (95% CI = 29.9-44.1%,) and 67.0% (95% CI = 58.7-74.7%) in patients with end-stage renal disease according to the objectively measured and self-reported CHS criteria, respectively,[34] and pooled mean prevalence of 52.3% (95%CI=37.9%-66.5%) in nursing home patients.[35]

It is of note that approximately 30% of patients with Alzheimer's disease were classified as physically robust with no frailty criteria components. Similar to the general elderly population,[36] frailty status changed dynamically as shown in a longitudinal study examining the frailty transition over one year among cognitively impaired community-dwelling older people.[37] In this study, frailty worsened in almost half of patients with mild to moderate Alzheimer's disease while approximately 17% of them improved their frailty status.[37] These findings suggest that frailty could potentially be targeted by interventions, such as an exercise program,[38; 39] to reduce related adverse outcomes[27; 30] in frail individuals with Alzheimer's disease.

Frailty and Alzheimer's disease share multiple etiologies, features, and related factors. For example, both frailty and Alzheimer's disease share a wide range of risk factors, including advanced age, female gender, low physical activity, low education, low wealth, depression, diabetes, and inflammation.[40; 41] Both entities are also associated with adverse health outcomes. Although frailty and Alzheimer's disease do not co-exist in all cases, multiple shared factors, a high co-occurrence rate, and apparent bidirectional causal associations may raise the possibility that frailty and Alzheimer's disease may have the same pathophysiology. Recent studies from the Rush Memory and Aging Project showed novel associations of Alzheimer's disease pathology with frailty.[42; 43] Postmortem Alzheimer's disease pathology has been significantly associated with a presence of frailty proximate to death[42] as well as a more rapid progression of frailty before death.[43]

The findings of this review should be interpreted with caution due to some limitations. First, the true prevalence of frailty among patients with Alzheimer's disease is expected to be much higher as end-stage patients may not be able to participate in studies or perform

measurements of physical frailty components due to severe cognitive and/or physical limitations. Three of the five included studies excluded patients with severe cognitive impairment: Mini-Mental State Examination (MMSE)<10 or Clinical Dementia Rating (CDR)=3,[29] MMSE<18,[27] and MMSE<15,[30] while the other two studies did not make exclusion criteria based on disease severity.[28; 31] Therefore, generalization of the findings of the current review would be limited to older people with mild to moderate Alzheimer's disease. Second, the number of studies included in the meta-analysis was only five and sample sizes of these studies were small (n=38-207), leading to a wide 95% confidence interval of the pooled prevalence (15.7%-48.5%). Third, two studies[30; 31] classified frailty in a dichotomous manner (YES/NO) while the other three[27-29] classified in three categories (robust, pre-frail and frail). This could potentially cause a bias in overall prevalence of frailty.

This review is still useful as patients with mild to moderate Alzheimer's disease are often targeted in dementia research. Another potential limitation is that all studies included in the meta-analysis used modified versions of the frailty criteria apparently due to the availability of data, as is often the case with other frailty studies.[44] It should be noted that these modifications may have significant impacts on outcomes.[44]

This review's findings on frailty status in the Alzheimer's disease population are important for clinicians and researchers. Clinicians, especially primary care practitioners, are currently encouraged to identify dementia earlier in its trajectory,[45; 46] and should be aware that one in three cases perceived as mild to moderate will also have physical frailty features. Therefore, comprehensive assessment should be part of the dementia recognition process.[47] Furthermore, identifying high risk individuals with both Alzheimer's disease and frailty[27; 30] may contribute to better care because these patients could potentially be targeted for interventions, or offered palliative care if necessary.[48] Researchers studying interventions early in the dementia trajectory should also be aware that physical frailty may limit their interventions, such as an exercise program[49]. Future research is warranted to examine frailty status of patients with Alzheimer's disease in different disease stages, including those with severe cognitive impairment.

## **CONFLICTS OF INTEREST**

No authors report conflicts of interest.

## **ACKNOWLEDGEMENTS**

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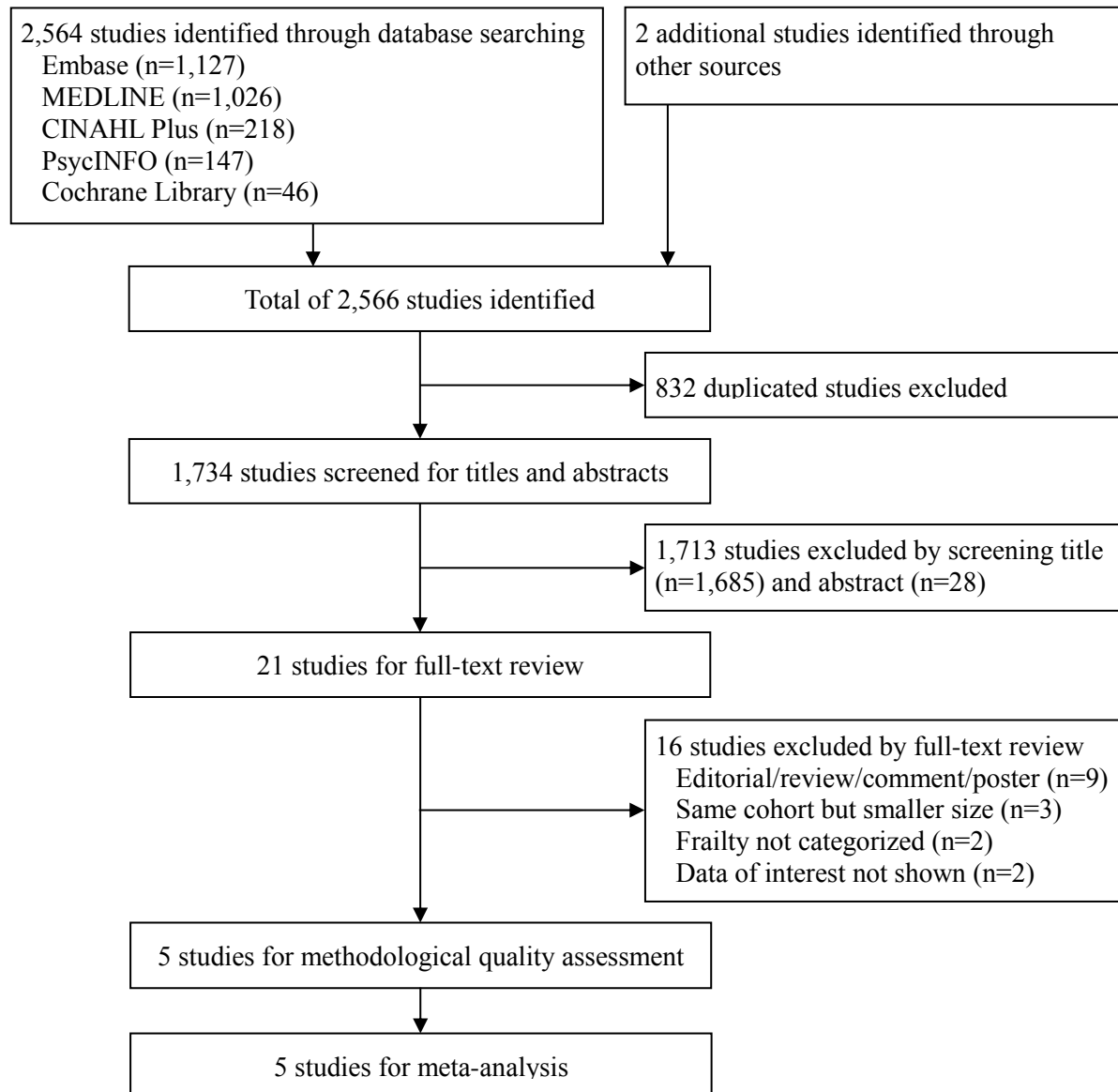
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**Figure 1.** Systematic review flow chart of study selection process



**Table 1.** Summary of studies on prevalence of frailty status in patients with Alzheimer’s disease.

Author/Study	Year	Location	Sample	Diagnostic criteria	Mean age* (range)	Female* (%)	Frailty criteria	Robust (%)	Pre-frailty (%)	Frailty (%)	Quality score†
Tay et al[31]	2016	Singapore	n=83 recruited from memory clinic Exclusion: possible AD, stroke, Parkinson’s disease, subdural hematoma, normal pressure hydrocephalus, brain tumor, hypothyroidism, B12 deficiency, hypercalcemia, any active neuropsychiatric conditions	NINCDS-ADRDA	76.6 (>55)	64.6%	mCHS	65 (78.3%)	-	18 (21.7%)	4/6
Kulmala et al[28] GeMS	2014	Finland	n=97 random sample from the community Exclusion: not documented	DMS-IV	82 (76-100)	69.6%	mCHS	23 (23.7%)	46 (47.4%)	28 (28.9%)	4/6
Oosterveld et al[29] 4C-Dementia	2014	Netherlands	n=207 recruited from memory clinics Exclusion: MMSE<10, CDR=3	NINCDS-ADRDA	75 (-)	57.7%	mCHS	82 (39.6%)	102 (49.3%)	23 (11.1%)	4/6
Bilotta et al[27]	2012	Italy	n=109 recruited from geriatric outpatient service Exclusion: MMSE<18	DMS-IV	82.8 (≥65)	77.1%	mSOF	25 (22.9%)	30 (27.5%)	54 (49.5%)	4/6
Solfrizzi et al[30] ILSA	2012	Italy	n=38 random sample from the community Exclusion: MMSE<15	NINCDS-ADRDA	73.1 (65-84)	45.2%	mCHS	19 (50.0%)	-	19 (50.0%)	5/6

\* Mean age and female proportion of cohort of interest, or entire cohort

† Methodological quality score.

4C-Dementia: Clinical Course of Cognition and Comorbidity-Dementia Study

AD: Alzheimer’s disease

CDR: Clinical Dementia Rating

DMS: Diagnostic and Statistical Manual of Mental Disorders

GeMS: Geriatric Multidisciplinary Strategy for the Good Care of the Elderly Study

ILSA: Italian Longitudinal Study on Aging

mCHS: Modified Cardiovascular Health Study criteria

MMSE: Mini-Mental State Examination

mSOF: Modified Study of Osteoporotic Fractures frailty index

NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer’s Disease and Related Disorders Association

Association

**Table 2.** Methodological quality of the included studies according to a tool for critically appraising studies of prevalence or incidence of a health problem.\*

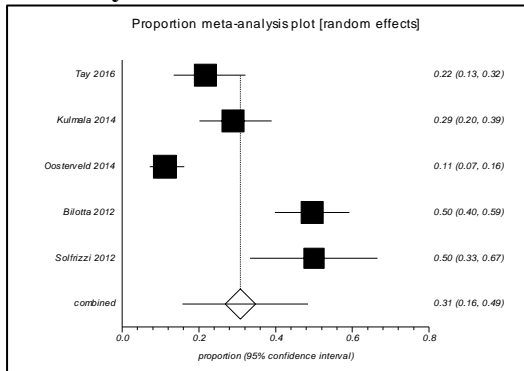
Study	1	2	3	4	5	6	Quality score
Tay et al	1	1	0	1	1	0	4/6
Kulmala et al	1	1	0	1	1	0	4/6
Oosterveld et al	1	1	0	1	1	0	4/6
Bilotta et al	1	1	0	1	1	0	4/6
Solfrizzi et al	1	1	0	1	1	1	5/6

\*

- 1) Are the study design and sampling method appropriate for the research question?
- 2) Is the sampling frame appropriate?
- 3) Is the sample size adequate?
- 4) Are objective, suitable and standard criteria used for measurement of the health outcome?
- 5) Is the health outcome measured in an unbiased fashion?
- 6) Is the response rate adequate? Are the refusers described?

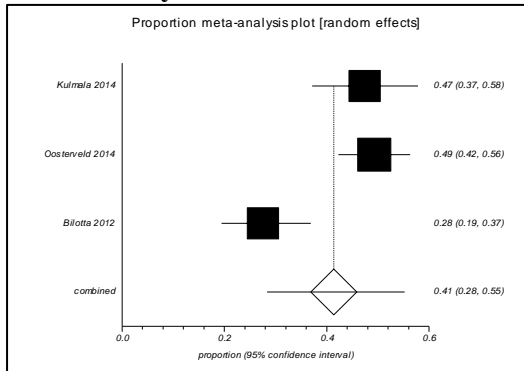
**Figure 2.** Forest plots of prevalence of (A) frailty, (B) pre-frailty, and (C) robustness among patients with Alzheimer’s disease.

**A Frailty**



Pooled prevalence: 31.9% (95%CI=15.7%-48.5%)  
 Heterogeneity:  $p < 0.0001$ ,  $I^2 = 94.1\%$

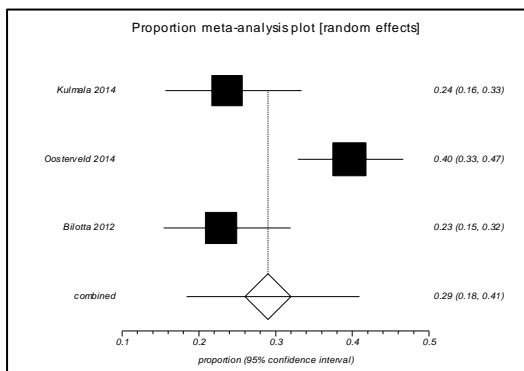
**B Pre-frailty\***



\* Only studies that provided three frailty categories (robust, pre-frail, and frail) were included.

Pooled prevalence: 41.4% (95%CI=28.3%-55.2%)  
 Heterogeneity:  $p = 0.0004$ ,  $I^2 = 87.0\%$

**C Robust\***



\* Only studies that provided three frailty categories (robust, pre-frail, and frail) were included.

Pooled prevalence: 29.0% (95%CI=18.4%-40.9%)  
 Heterogeneity:  $p < 0.001$ ,  $I^2 = 84.2\%$