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A Tune in “A Minor” Can “B Major”: A Review of Epidemiology, Illness Course, and Public Health Implications of Subthreshold Depression in Older Adults

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Abstract

BACKGROUND—With emphasis on dimensional aspects of psychopathology in development of the upcoming DSM-V, we systematically review data on epidemiology, illness course, risk factors for, and consequences of late-life depressive syndromes not meeting DSM-IV-TR criteria for major depression or dysthymia. We termed these syndromes subthreshold depression, including minor depression and subsyndromal depression.

METHODS—We searched PubMed (1980–Jan 2010) using the terms: *subsyndromal depression*, *subthreshold depression*, and *minor depression* in combination with *elderly*, *geriatric*, *older adult*, and *late-life*. Data were extracted from 181 studies of late-life subthreshold depression.

RESULTS—In older adults subthreshold depression was generally at least 2–3 times more prevalent (median community point prevalence 9.8%) than major depression. Prevalence of subthreshold depression was lower in community settings versus primary care and highest in long-term care settings. Approximately 8–10% of older persons with subthreshold depression developed major depression per year. The course of late-life subthreshold depression was more favorable than that of late-life major depression, but far from benign, with a median remission rate to non-depressed status of only 27% after ≥1 year. Prominent risk factors included female gender, medical burden, disability, and low social support; consequences included increased disability, greater healthcare utilization, and increased suicidal ideation.

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Conflict of Interests

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LIMITATIONS—Heterogeneity of the data, especially related to definitions of subthreshold depression limit our ability to conduct meta-analysis.

CONCLUSIONS—The high prevalence and associated adverse health outcomes of late-life subthreshold depression indicate the major public health significance of this condition and suggest a need for further research on its neurobiology and treatment. Such efforts could potentially lead to prevention of considerable morbidity for the growing number of older adults.

INTRODUCTION

With the introduction of the DSM-III, psychiatry increased reliability of its diagnoses, including major depressive disorder (MDD) (Judd et al., 1994). The establishment of boundaries at which the frequency, duration, or severity of symptoms crossed a “threshold” sufficient to be labeled psychopathology was not simple, however. When possible, thresholds were based on empirical data, but otherwise, non-empirical “expert opinion” was involved in separating the “ill” from the “well.” With emphasis on dimensional aspects of psychopathology in development of the upcoming DSM-V, now may be an opportune time to explore the merits of better defining various continua of disorders such as depression. Subthreshold depression (SubD) has sometimes been divided into distinct categories (e.g. minor depression [MinD], recurrent brief depression, and subsyndromal depression [SSD]), but at other times studied as a single entity. Based on the diagnostic criteria used in studies, overlap among these constructs is common. We exclude dysthymia (DYS) as a type of SubD because it has well-defined DSM-IV-TR (First et al., 2002) criteria, and most SubD studies do not include it.

In 1992, Wells et al. (1989) reported that depressive symptoms not qualifying as MDD were associated with more social disability than many medical illnesses. Soon thereafter, Judd et al. (1994), in analyses from the Epidemiological Catchment Area (ECA) study (1982), reported a one-month prevalence of SSD in the general adult population of 11.8%. DSM-IV later listed criteria for MinD among its research diagnostic criteria in the section on Depression Not Otherwise Specified. These were similar to those for MDD except requiring only 2–4 symptoms and no prior history of MDD; however, subsequent research has shown that DSM-defined MinD misses a substantial number of people who suffer morbidity from other variants of SubD. For instance, Judd et al. noted that among the SubD subjects in the ECA study, less than a third met criteria for MinD because neither depressed mood nor anhedonia (MDD Criterion A symptoms) were present (Judd et al., 1994). The investigators found virtually no differences between SubD subjects with versus without Criterion A symptoms. Angst and colleagues (1990) proposed another variant of SubD—recurrent brief depression, in which the only reason for failing to meet MDD criteria was that symptoms did not persist uninterrupted for two consecutive weeks.

Despite variable definitions and criteria, “non-major” depressions consistently exact major consequences on affected individuals (e.g. increased disability, poorer quality of life) and on society (e.g. increased healthcare costs) (Broadhead et al., 1990; Hybels et al., 2001; Sptizer et al., 1995; Xavier et al., 2002; Koenig, 1998). The concept of SubD resonated strongly in geriatric psychiatry (Jeste et al., 1999; Jeste et al., 2005), along with a speculation that MDD prevalence among older adults was inaccurate in the ECA study because of diagnostic ascertainment procedures (Judd and Akiskal, 2002). Re-analyzing the ECA data, Judd and Kunovac (1998) found that among adults ≥ 65 years old, SubD (MinD + SSD) prevalence was 31.1%, versus 6.3% for MDD—a fivefold difference.

Given the preponderance of SubD compared to MDD in older adults and the increasing research on late-life SubD, we believe an updated review of SubD in older adults is warranted. Specifically, we focus on the following aspects of late-life SubD, for which we

know of no recently published comprehensive review: epidemiology, longitudinal time course, risk factors and public health consequences.

METHODS

We searched PubMed (1980– January 2010) using combinations of the following search terms: Group (A) *subsyndromal depression*, *subthreshold depression*, and *minor depression* with Group (B) *elderly*, *geriatric*, *late-life*, and *older adult*. Additional articles were identified via manual review of references in articles from database searches. We extracted data from articles in English conducted among older adults (age ≥ 55 years) that focused on any depressive condition with proposed criteria other than MDD, DYS, or bipolar depression. We included data on epidemiology only from studies with sample size ≥ 100 . When two or more categories of SubD were assessed in the same study (e.g., MinD and SSD), we added their prevalences for a single estimate of SubD prevalence. We also calculated the prevalence ratio of SubD:MDD, and when available, calculated female:male prevalence ratios.

RESULTS

We identified 153 unique, potentially relevant articles by database searches (Figure 1). Although we used search terms *geriatric*, *older adult*, and *late life* for thoroughness, these terms yielded no articles other than those discovered with the search term *elderly*, hence the omission of these other search terms in Figure 1. An additional 28 studies of interest were identified via manual review of database-generated articles.

EPIDEMIOLOGY

Community-based Studies—Table 1 summarizes epidemiological studies of late-life SubD. Twenty of the 37 investigations were at least partially community-based; five of these assessed mixed community-dwelling (CD) and long-term care (LTC) populations. Two studies (Kvaal et al., 2008; Geiselmann and Bauer, 2000) did not report what proportion of participants was CD versus LTC and were, therefore, excluded from composite data on CD epidemiology of SubD. In contrast, the other two mixed studies were included because one was predominantly community-based (87%) (Paivarinta et al., 1999) and the other reported findings which allowed separate analysis of CD vs. LTC data (Østbye et al., 2005); the fifth such study, while reporting the breakdown of CD vs. LTC participants, was excluded based on its unorthodox methodology (Steffens et al., 2009). Twelve of the 17 CD studies included for epidemiological estimates reported a point prevalence. SubD point prevalence in the community ranged from 4.0–22.9% (median prevalence 9.8%). All CD studies reported MDD or “syndromal depression” prevalence as well, and the ratio of SubD:MDD prevalence ranged from 1.1 to 6.9 (median 2.5). Studies assessing more than one variant of SubD (e.g., MinD and SSD) yielded higher than the median prevalence rates of SubD and ratios of SubD:MDD. The female preponderance seen in MDD (2:1) appeared somewhat reduced among CD older adults with SubD, with female:male prevalence ratios ranging from 1.0 to 2.4:1 (median 1.6:1), although many studies did not report these data.

Four community-based investigations assessed 1-month prevalence: (a) SubD 31.1% (Judd and Kunovac, 1998) (DSM-IV MinD 13% + Judd et al. criteria (Judd et al., 1994) SSD 18.1%), (b) 16.5% SSD (Geriatric Mental State defined [a semi-structured interview]) (Geiselmann et al., 2001)—similar to SSD prevalence in the prior study using Judd et al. criteria, (c) 12.9% MinD (Beekman et al., 1995)—virtually identical to MinD prevalence in the first study, and (d) 8.8% SSD (Chen et al., 2007) (using the more stringent criteria of Lavretsky and Kumar (2002)).

Primary Care Studies—The prevalence of late-life SubD appears to be lower in the community as compared to primary care (PC) and inpatient hospitals, and is highest in institutional settings, similar to the epidemiological pattern of MDD. However, since these numbers are drawn from different populations, it is not conclusive that this represents a progressive increase in prevalence across such settings. Lyness and colleagues pioneered research of late-life SubD in PC settings (Lyness et al., 2009; Lyness et al., 2007; Lyness et al., 1999), with three studies reporting SubD point prevalence among older adults ranging from 15.1% to 35.9%. Two of these studies noted similar prevalences of DSM-defined MinD (5.2%–6.3%). All three studies assessed SSD, although with variable criteria; two evaluated SSD based on Hamilton Depression Rating Scale (HAMD) scores (>10) and reported prevalence of 9.9% and 20.4%. The latter prevalence (termed SSD-“A” in this study) is from a novel study comparing three different criteria for SSD, with the other two criteria being those espoused by Judd et al. (1994) (SSD-“B”: prevalence 16.2%), and alternative criteria proposed by Lyness et al. (SSD-“C”: prevalence 28.1%). (See Table 1 footnotes for details of these criteria). The final Lyness et al. PC study reported SubD prevalence as 35.9%, combining MinD, SSD-“C”, and also DYS; the individual prevalence of each diagnosis was not reported, but including DYS and using the most inclusive criteria for SSD (SSD-“C”) probably elevated prevalence rates (Lyness et al., 2009). Using a median prevalence of ~20% for SSD in combination with a prevalence of ~5% for MinD, SubD prevalence in PC is approximately 25% among Caucasian Americans. The SubD:MDD ratio among the Lyness et al. studies ranged from 2.3 to 7.5:1. The female:male prevalence ratio (2.1–2.3:1 based on 2 studies), was higher than that seen in the community—perhaps reflecting greater care-seeking behaviors by women.

In other American PC studies (Williams et al., 1995; Aranda et al., 2001) which included ≥50% Mexican-Americans or exclusively Latinos, the SubD prevalence (16.0–20.1%) and ratio of SubD:MDD (4.0–5.0:1) fell within the range reported in the aforementioned, predominantly Caucasian samples, despite use of more restrictive criteria.

An Italian PC study (Berardi et al., 2002) assessed point prevalence of International Classification of Disease (ICD) “current depressive episode” (CDE) (similar but not identical to DSM MDD) and found CDE almost twice as common as SSD. While not as drastically different from American PC studies, a Dutch PC study (Licht-Strunk et al., 2005) reported a notably lower point prevalence of SubD (10.2%) than that observed in American PC clinics. Differences in PC settings in Europe and the US, and absence of overlap in SubD criteria between American and European PC studies may partially explain these disparate epidemiological results.

Medical Inpatient Studies—We found only four epidemiological studies of SubD among older medical inpatients. Three of these reported higher point prevalences of SubD than MDD; the magnitude of difference was lower than in CD and American PC studies, likely because three of the four studies (Koenig et al., 1991; Koenig, 1997; McCusker et al., 2005) assessed MinD only. A fourth study by Schneider et al. (2000) examined SSD prevalence (determined by an ICD checklist) using inclusive versus exclusive approaches to depression diagnosis. The prevalences of MinD in two studies and SSD diagnosed via an inclusive approach were remarkably similar (29.2%, 27.9%, and 32.1%). SSD diagnosed via an exclusive approach decreased the prevalence (17.6%). The McCusker et al. (2005) study was anomalous in finding significantly higher rates of MDD than MinD in older medical inpatients, reporting a prevalence of MinD among patients in two hospitals of 7.9–9.4%. Notably, the prevalence of MDD varied by more than 30% between the two hospitals, indicating possible methodological issues in diagnostic ascertainment. Ratios of SubD:MDD in the first three studies ranged from 1.25 to 2.2:1. The SSD study was the only one to provide a female:male prevalence ratio (1.9:1) (Schneider et al., 2000).

Long-term Care (LTC) Studies—Several reports examined SubD point prevalence in LTC settings. Five of seven studies assessed MinD, although only two used DSM or Research Diagnostic Criteria (Jongenelis et al., 2004; Østbye et al., 2005; Morrow-Howell et al., 2008; Teresi et al., 2001; Parmelee et al., 1992; Parmelee et al., 1989). The prevalence of MinD ranged from 4.0% to 30.5 %, with the more rigorous criteria yielding similar rates of 16.8% and 14.1%. Østbye et al. (2005) reported a puzzling prevalence (4%) of MinD—lower than that seen in many CD studies, possibly due to lack of a singular focus on LTC or differences in the natures of the “institutions.”

The two investigations (Teresi et al., 2001; Jongenelis et al., 2004) with rigorous criteria for MinD along with one other American study assessed SSD or SubD defined based on symptom scale thresholds, and “non-MinD” SubD prevalence ranged from 19% to 44%; thus, in combination with rigorously defined MinD prevalences, approximately 33–61% of LTC residents experienced SubD at any given point in time. While many factors of institutional living may account for this high prevalence, it should be noted that most LTC studies did not exclude persons with cognitive disorders, which are prevalent in LTC and, as discussed later, themselves a risk factor for depressive disorders. Five of seven LTC studies found SubD more common than MDD, with SubD:MDD ratios ranging from 0.52 to 4.7:1 (median 2.5:1).

Only a few other settings have received epidemiological study of late-life SubD. RDC-defined MinD prevalence among older persons in hospice was reported as 9.2% (versus 16.9% for MDD); employing “Endicott criteria” (Endicott and Spitzer, 1979), which focus primarily on psychological depressive symptoms because neurovegetative symptoms among hospice patients are rampant, point prevalence was 12.3% for MinD and 10.3% for MDD (Chochinov et al., 1994). Three studies among older home healthcare recipients reported similar point prevalence of DSM-defined MinD (7.0, 8.2, and 10.8%) (Yewdell and Bennink, 1990; Fyffe et al., 2004).

LONGITUDINAL ILLNESS COURSE

Risk of Developing Major Depression—SubD diagnosed cross-sectionally may encompass a heterogeneity of depressive disorders, necessitating longitudinal data to yield a dynamic view of the condition over time. A focus of SubD illness course has been whether SubD serves as a prodrome to MDD. Two large studies in general adult populations found one-year and two-year rates of conversion to MDD to be 10% and 25%, respectively (Broadhead et al., 1990; Wells et al., 1992). Cuijpers et al. reviewed studies assessing risk of developing MDD among community-dwelling (CD) adults of all ages with SubD and found the relative risk (RR) ranged from 1.15 to 9.73 (median 4.43) (Cuijpers and Smit, 2004).

In older adults, two community-based Dutch investigations assessed MDD risk in late-life SubD. A six-year study reported that 20% of older adults with SSD (symptom scale threshold defined) developed a DSM-IV mood disorder: MDD (5.8%), DYS (12.3%), or comorbid MDD/DYS (1.9%) (Cuijpers et al., 2006). Data did not permit RR calculation, and it was not clear whether being diagnosed with SSD changed longitudinal depression treatment. The other Dutch study reported the 3-year RR of developing MDD among older adults with SSD (Geriatric Mental State defined) versus non-depressed (ND) peers to be 2.43 (3-year absolute risk 29.3%) (Schoevers et al., 2006). The absolute risk of 29.3% is significantly higher than the prior study, possibly due to different criteria for SSD, but this latter rate of approximately 10% per year is similar to reports among general adults cited above.

Several American investigations in PC settings examined future MDD risk in late-life SubD. Using PROSPECT study data, Lyness et al. (2006) reported that 8.8% of older adults with

MinD or SSD had MDD after one year, consistent with a 16.2% two-year absolute risk of MDD in another PC study of late-life SubD (SSD + MinD) (Cui et al., 2008). These results were similar to the 10%/year conversion rate from SubD to MDD in another PC study (versus 2%/year MDD incidence among ND peers) (Lyness et al., 2002). Another group of investigators followed older adults in PC for 18 months, and among those with Structured Clinical Interview for DSM-IV (SCID) diagnosed MinD (with or without past MDD), 25% had developed MDD at study end. This yields a somewhat higher annual rate of conversion of 16.7% from SubD to MDD, perhaps because in contrast to the three prior studies, this study included only MinD—not any form of SSD (Vuorilehto et al., 2009). Lyness et al. (2009) later examined the risk of developing MDD in another PC sample of older adults with SubD (MinD + SSD) or DYS. Odds ratios (OR) for MDD diagnosis at one year compared to ND older adults were 12.1 for MinD and 6.1 for SSD. Another PC study addressed another issue—whether outcomes differed according to past history of MDD (Chopra et al., 2005). At three months, absolute risk of developing MinD, DYS, or MDD was 24.3% among SSD subjects with a history of MDD, significantly higher than that among those without prior MDD (10.1%), perhaps implying SSD was residual MDD in the former sub-sample.

Research on longitudinal MDD risk in other populations is limited. One study assessed post-myocardial infarction (MI) patients for MinD and noted that, after three months, 14% of persons with MinD had MDD versus only 6% among persons ND at baseline (Schleifer et al., 1989). Another investigation of persons with coronary heart disease (CHD) found that of the 17% of persons with MinD at baseline, 42% developed MDD at 1-year follow-up, indicating CHD may increase the risk for conversion from MinD to MDD above the average rate of 8–10% per year described above (Hance et al., 1996). Lastly, a study among senior community residents reported that among those with baseline MinD in “congregate apartment living,” 10% had MDD one year later, versus 23% among persons in traditional LTC (Parmelee et al., 1992).

Stability of longitudinal diagnosis—Aside from future risk of MDD, other longitudinal research on late-life SubD has focused on diagnostic stability. In the seminal Longitudinal Aging Study Amsterdam (LASA) (Beekman et al., 2002), CD older adults with MDD, DYS, and SubD (defined by Center for Epidemiological Studies Scale for Depression threshold scores) were evaluated at 14 time points over six years. Those with “double depression” (MDD/DYS) fared the worst, with only 5% achieving remission. While SubD had the best prognosis among the diagnoses assessed (26% remission rate), 61% of older adults with SubD had a chronic or chronic-intermittent course. Among PC patients in whom MinD and SSD were combined as a single category of SubD, stability of diagnosis at one year was similar to the LASA results (62–70%), with only 21.6–25.4% of older adults with SubD qualifying as ND after one year (Cui et al., 2008; Lyness et al., 2009). Strikingly similar numbers were reported from a very different population of mostly urban, CD African-Americans (65%) of Caribbean heritage (Cohen et al., 2009). SSD was defined by a score of 8–15 on the Center for Epidemiological Studies Scale for Depression (CES-D), whereas scores ≥ 16 were considered “syndromal depression” (SD). After 3 years, only 18% of those with baseline SSD were ND, while 59% had a stable diagnosis of SSD. Nonetheless, more of those with baseline SD had SD (50%) at follow-up than those with baseline SSD (23%). Study of SubD’s longitudinal course in PC has yielded a somewhat more favorable prognosis than in the community, although the number of studies are limited in both settings. One PC study reported that 48.8% of those with MinD/ SSD were ND at one year, still leaving more than half of such persons with depressive symptoms (Lyness et al., 2002). Another study in PC found a similar remission rate of 55% for MinD at 18-month follow-up (versus 38% remission for MDD) (Vuorilehto et al., 2009).

The longitudinal course of SubD in medical inpatients has been examined with variable results. A study among older medical inpatients indicated a fluctuant 1-year course for those with baseline MinD—4% maintained a stable diagnosis of MinD, 28% maintained stable ND recovery, and 68% vacillated between MDD, MinD, and ND (Cole et al., 2006). However, another investigation showed a relatively stable 1-year symptom course—measuring stability of depressive symptom severity (“minimal,” “mild,” or “moderate-severe” on the HAMD), rather than tracking categorical diagnoses (McCusker et al., 2007). Another study of inpatients with congestive heart failure reported more favorable rates of remission, 65% for MinD and 57% for MDD (statistically equivalent), but a trend for faster recovery time for MinD (3 weeks) versus MDD (20 weeks) (Koenig, 1998). Older inpatients with post-MI MinD had an intermediate rate of being ND at 3-month follow-up (64%) compared to those with post-MI MDD (23% ND) and those ND at baseline (83% ND) (Schleifer et al., 1989). A stable diagnosis of MinD occurred in only 22% of cases.

Evidence from other older populations supports the notion that MinD has a more favorable prognosis than MDD but that its course varies and is certainly less favorable than for ND elders. Among LTC residents, the rate of being depression-free one year after baseline assessment was 88% for a ND group versus only 3.3%–3.6% for those with MDD or MinD at baseline (Parmelee et al., 1992). In contrast, when screening new admissions to LTC (undergoing the acute stressor of moving), 45% of those who were depressed at baseline (75% of whom had SubD) were ND one year later (Morrow-Howell et al., 2008).

The longitudinal course of SubD has also been studied in the spousally-bereaved. Evaluations conducted 2–25 months after the loss showed that prognosis varied from best to worst in the following order: ND→SSD→MinD→MDD (Zisook et al., 1997). Over nearly 2 years, widows/widowers with baseline diagnoses in parentheses spent the following percentage of time non-depressed—84% (ND), 61% (SSD), 47% (MinD), and 24% (MDD) versus this percentage of time in major depression—2.4% (ND), 6.4% (SSD), 6.6% (MinD), 38.4% (MDD). Despite having a better prognosis than MDD patients, spousally-bereaved older adults with SubD still spent more than 40% of their time in a persistent state of SubD over 2 years. In another at-risk group—persons with dementia—23.6% of patients had MinD at baseline, and they spent on average 25% of the next 9 months with symptomatic depression, although a significant minority had more persistent depressive symptoms (9.5% with MDD and 24% with ≥6 months of significant depression) (Ballard et al., 1996). Altogether, prospective studies of the course of late-life SubD of at least one year duration reported rates of remission to ND status ranging from 3.6 to 52% (median 27%).

HEALTH OUTCOMES: RISK FACTOR, CONSEQUENCE, OR BOTH?

Studies have demonstrated associations between SubD and multiple negative medical and psychosocial conditions in addition to MDD. A majority of investigations have been cross-sectional, limiting cause-and-effect interpretations. In some cases, it is likely that a certain adverse condition (e.g., functional disability) is *both* a risk factor for and a consequence of SubD, interacting in a vicious feed-forward cycle. Below, we first discuss cross-sectional evidence linking SubD with adverse health conditions, and subsequently we consider more conclusive prospective studies.

Cross-sectional Associations—Even in cross-sectional studies, certain variables are clearly risk factors rather than consequences, e.g. gender. Many of the epidemiological studies already summarized indicated female gender as a risk factor for late-life SubD (Beekman et al., 1995; Kvaal et al., 2008; Østbye et al., 2005; Xavier et al., 2002; Hybels et al., 2001; Lyness et al., 2007; Cohen et al., 2005; Schoevers et al., 2006). Other variables

reported as risk factors include past history (Beekman et al., 1995; McCusker et al., 2005) and family history (Beekman et al., 1995) of depression/psychiatric illness.

Certain medical illnesses associated with MDD have been identified as possible risk factors for SubD, e.g. visual impairment (Horowitz et al., 2005), end-stage renal disease requiring hemodialysis (Drayer et al., 2006; Hinrichsen et al., 1989) Parkinson's disease (Tandberg et al., 1996; Ehrt et al., 2007; Costa et al., 2006; Starkstein et al., 2008), cardiac disease/CHD (Penninx et al., 2001; Hance et al., 1996) and stroke (Eastwood et al., 1989; Saxena et al., 2008; Brodaty et al., 2007). Cognitive disorders also increase risk of SubD; four studies of cognitively impaired older adults (two with Alzheimer's disease, two with mild cognitive impairment) reported similar point prevalences of MinD—17.2%, 26%, 26.5%, and 27% (versus median community prevalence of 9.8%) (Lyketsos et al., 1997; Kumar et al., 2006; Gabryelewicz et al., 2004; Starkstein et al., 2005). Although depressive symptoms likely result from neurobiological changes in dementia (Meeks et al., 2006; Brodaty et al., 2007), a reverse relationship in which depression is a possible risk factor for cognitive decline (Butters et al., 2008) complicates the interpretation of directionality (Saxena et al., 2008).

Variables cross-sectionally associated with late-life SubD which may be antecedents, consequences, or both include the following: (a) being unmarried (Schneider et al., 2000; Beekman et al., 1995; Hybels et al., 2001), (b) low socioeconomic status (Blazer and William, 1980; Adams and Moon, 2009; Mechakra-Tahiri et al., 2009), (c) Lower education (Blazer and William, 1980; Adams and Moon, 2009) (d) executive function and verbal recall impairments (McCusker et al., 2005; Parmelee et al., 1992; Xavier et al., 2002; Chuan et al., 2008; Elderkin-Thompson et al., 2003; Elderkin-Thompson et al., 2006), (e) increased medical burden (Beekman et al., 1995; Parmelee et al., 1992; Chuan et al., 2008; Geiselman et al., 2001; Hybels et al., 2001; Lyness et al., 2007; Penninx et al., 1999), (f) disability (Beekman et al., 1995; McCusker et al., 2005; Parmelee et al., 1992; Schneider et al., 2000; Chuan et al., 2008; Eastwood et al., 1989; Geiselman et al., 2001; Hybels et al., 2001; Lyness et al., 1999; Lyness et al., 2007; Penninx et al., 1999), (g) decreased social support/loneliness/conflicted relationships (Beekman et al., 1995; Adams and Moon, 2009; Mechakra-Tahiri et al., 2009; Morrow-Howell et al., 2008; Blazer and William, 1980; McCusker et al., 2005; Schneider et al., 2000; Hybels et al., 2001; Pasternak et al., 1992) and (g) negative life events and loss (Beekman et al., 1995; Adams and Moon, 2009; Morrow-Howell et al., 2008; Ormel et al., 2001). These are consistent with a recent meta-analysis of risk factors for late-life depression (variably defined, not generally referring to SubD) (Cole, 2005). Other reported associations include decreased quality of life (Chachamovich et al., 2008; Geiselman and Bauer, 2000; Williams et al., 1995), more negative attitudes toward aging (Chachamovich et al., 2008), personality traits such as increased neuroticism (Lyness et al., 2002; Weiss et al., 2009; Aben et al., 2002) or decreased conscientiousness (Weiss et al., 2009), and lower intrinsic religiosity (Koenig et al., 1998).

Prospective Studies: Risk Factors—A prospective investigation has identified medical burden, functional disability, and decreased social support as risk factors for persistence or worsening of MinD among older medical inpatients followed for three months (Koenig et al., 2006). Similarly, among depressed medical inpatients (37% with MinD), negative life events predicted lack of recovery at 1-year (Koenig, 1998). Cui et al. (2008) conducted a 2-year observational cohort study among older PC patients with MDD, SubD (SSD + MinD), and ND. The authors identified six different illness trajectories, two being germane to this discussion. One trajectory involved ND→SubD; risk factors for this outcome included medical burden and past depression history. Another trajectory was SubD→MDD, predicted by higher medical burden, greater disability, and less social support. These findings were partly replicated in a later study of SubD in PC patients—i.e.,

increased MDD risk and severity at one year predicted by more disability and less social support (Lyneess et al., 2009).

Prospective Studies: Consequences—Several prospective studies have demonstrated significant adverse public health outcomes in late-life SubD. Four of six relevant studies reported that late-life SubD increased healthcare utilization. Supportive reports included: (a) 1-year follow-up of medical inpatients with either MDD or MinD (Koenig, 1998), (b) 10-year follow-up of CD older adults with SubD, who used more home health and social services than ND peers (Beekman et al., 1997), (c) a study of stroke rehabilitation patients with MDD or MinD, who had longer hospital stays than ND controls (Eastwood et al., 1989), and (d) a 5-month follow-up of older medical inpatients assessing mixed symptoms of depression and anxiety in which subthreshold symptoms increased healthcare costs (Creed et al., 2002).

At the individual level, prospective investigations of late-life SubD have identified the following adverse consequences in comparison with ND older adults: (a) increased cognitive impairment at 1-year follow-up among cognitively intact medical inpatients with MinD (Han et al., 2008) as well as elevated risk of dementia or cognitive disorder NOS over 3 years in a sample of primary care outpatients (Boyle et al., 2010) and (b) poorer physical health among CD older adults with MinD in the 10-year LASA study (Beekman et al., 1997). Perhaps most impressive is the evidence that SubD increases risk for future functional disability. This was demonstrated in at least eight studies, with findings such as the following: (i) slower recovery among hospitalized rehabilitation patients (Allen et al., 2004), (ii) increased bed-days and decreased activity due to health in the LASA study (Beekman et al., 1997), (iii) more impairment in activities of daily living (ADLs) among CD older adults and those in home healthcare (Li and Conwell, 2009; Hybels et al., 2009; Weinberger et al., 2009; Hybels et al., 2009), (iv) during a 4-year study of CD older adults, objective decline on physical performance tests (e.g., balance and walking speed) that correlated linearly with depression severity beginning with “subclinical” levels of depression (Penninx et al., 1998), and (v) over nine years of follow-up, a linear relationship between depression severity as measured by the CES-D and progression to mild disability starting with CES-D scores of zero, as well as CES-D scores (10–19) usually considered under the threshold for significant depression predicting mild and severe disability in ADLs (Barry et al., 2009).

There are mixed results regarding increased mortality with SubD. SubD increases suicidal ideation (Angst et al., 1990; Chopra et al., 2005; Montross et al., 2008), and one retrospective “psychological autopsy” study found that among completed suicides versus control subjects, OR for completed suicide among persons age ≥ 75 was significantly elevated (OR=42.3) for those diagnosed by collateral history with MinD (Waern et al., 2003). In another study in Sweden conducted among older persons seeking treatment for suicide attempts in emergency rooms, MinD was associated with elevated risk (OR=2.6) (Wiktorsson et al., 2010). Depression has been linked to increased non-suicide mortality among several late-life disorders (Katon et al., 2008). Of these, CHD (Whang et al., 2009; Williams et al., 2004) has received the most attention. Three studies (Carney et al., 2008; Romanelli et al., 2002; Penninx et al., 2001) reported that older adults with MinD vs. ND peers had increased CHD-related mortality (OR 4.8, hazard ratio [HR] 1.7, and RR 2.1) with follow-up periods from 4 months to 5 years. In a 6–8 year cohort study of older persons after coronary artery bypass graft (CABG), DSM-IV MinD increased long-term risk for “coronary events” (angina, MI, or cardiac death) (Rafanelli et al., 2006), whereas a similar study among older adults *without* baseline CHD, found no increase in ischemic coronary events among persons with SubD (symptom-scale defined) followed on average for 7.2 years (Bremmer et al., 2006). Similarly, MinD failed to predict mortality among patients

with congestive heart failure over a 2.5-year period (Faller et al., 2007). However, another study found that CHF patients with MinD had a significantly increased risk of adverse cardiovascular events (HR = 4.36) at 2-month follow-up, while those with MDD did not (Rafanelli et al., 2009).

In a study of mortality among patients with diabetes mellitus, Lin et al. (2009) noted that in a 5-year cohort, after adjustment for demographics, clinical characteristics, health habits and treatment-related measures, MinD was associated with increased all-cause mortality (HR = 1.52). In a cross-sectional study of older adults with diabetes mellitus, Egede et al. (2009) noted that presence of MinD or MDD was associated with poor adherence to self-care recommendations (most notably physical activity and smoking cessation) as well as lower scores on quality of care indicators (notably receipt of flu shots and receipt of eye examinations). One could posit such poor self-care is at least one significant mediator of the increased risk of mortality in diabetes patients with MinD in the prior study.

Penninx et al. (1999) as part of the LASA study examined overall mortality risk among older adults with MDD and “MinD” (defined by symptom scale thresholds) longitudinally for approximately 50 months. After adjusting for possible confounds, the increased risk was significant for MDD (RR 1.68) and for males with MinD (RR 1.45). There was no link between MinD/depressive symptoms and mortality in two studies of LTC residents, whereas MDD increased mortality in both studies (Rovner et al., 1991; Parmelee et al., 1992). A similar lack of an association between late-life SubD and mortality has been reported in other studies of CD older adults and older medical inpatients, with one report even showing lower mortality among women with SubD versus ND women (Hybels et al., 2002; McCusker et al., 2006). However, several studies of SubD in older adults with specific medical conditions (e.g. diabetes mellitus, dementia, end-stage renal disease, and stroke [2 studies]) have found that SubD significantly increased mortality (HR 1.7, OR 4.3, HR 4.1, OR 3.7, and HR 2.0, respectively) (Janzing et al., 1999; Drayer et al., 2006; Katon et al., 2005; Morris et al., 1993; Endicott and Spitzer, 1979).

DISCUSSION

The evidence reviewed above strongly suggests that late-life SubD, howsoever defined, is prevalent, worsens quality of life and health of older adults, and impacts healthcare systems via increased service utilization and cost expenditure. Epidemiological research on late-life SubD demonstrated a pattern observed in late-life MDD: increasing prevalence moving from community to PC to LTC settings (community [10%], PC [25%], medical inpatients [30% +], LTC [c. 45–50%]). SubD was consistently at least 2–3 times more prevalent than MDD across all settings. When gender data were reported, the female:male diagnostic ratio was similar to but perhaps slightly lower than the 2:1 ratio in MDD. When assessed simultaneously, SSD prevalence was generally higher than MinD prevalence. The most consistently identified risk factors for late-life SubD in prospective studies were increased medical burden, disability, decreased social support, female gender, and neurological illnesses (e.g. Parkinson’s disease, stroke, AD).

Research on the longitudinal course of late-life SubD indicates risk of developing MDD to be generally 8–10% per year, with possibly higher risk in LTC and among persons with CHD. Studies from various settings indicate the prognosis (e.g., odds of remission) are better for late-life SubD than for MDD, although a majority (median 73%) of older adults with SubD remained symptomatic during follow-up. Some studies indicated the diagnostic stability of late-life SubD categories was relatively low but did not suggest either that SubD has a benign course or that it is an invalid diagnosis. Indeed, a fluctuant course is similar to results from a study of the 12-year course of MDD among adults aged up to 79 which

demonstrated that affected persons were symptomatic 60% of the 12-year period, and when symptomatic, 73% met criteria for SubD, not MDD (Judd et al., 1998).

The negative health consequences associated with late-life SubD are on par with those seen in many chronic medical and psychiatric conditions, including increased healthcare utilization and expenditure, cognitive impairment, physical health decline, increased disability, and increased suicidal ideation. Most studies among general populations of older adults do not support an association between SubD and increased mortality, although SubD has been linked to increased mortality in certain medical conditions. Disability emerged as a robust risk factor for *and* consequence of late-life SubD. Please see Bruce (2001) for a review of the complex interplay between depression and disability.

Data also suggest that SubD exists on a spectrum with established depressive disorders (MDD and DYS). Similarities between late-life MDD and SubD have been demonstrated in gender ratio (Beekman et al., 1995), affective disorder family history (Beekman et al., 1995), and associations with a number of similar adverse outcomes (Hybels et al., 2001). Also, variables, such as cognitive impairments (Costa et al., 2006; Elderkin-Thompson et al., 2003), worse symptomatic and functional outcomes (Lyness et al., 2006), ADL impairments (Schneider et al., 2000), and lack of social support (McCusker et al., 2005), which were associated with late-life depression diagnoses, demonstrated levels of correlation with SubD intermediate between correlations reported for MDD and ND.

Some limitations of this review warrant discussion. We could not conduct a meta-analysis due to data heterogeneity (especially in the criteria used to define “less than major” depression) which complicated data synthesis. The DSM-IV criteria for MinD were the most replicable and consistent among the various criteria of SubD reviewed, although several studies did not apply these criteria rigorously. Aside from MinD, the most common diagnosis used was SSD, defined based on various criteria (Judd et al., 1994; Lavretsky and Kumar, 2002; Lyness et al., 2007), or scoring above an established threshold on a depression rating scale.

Concerns for the effects of heterogeneous SSD criteria on conclusions in this review are partially tempered by a study (Lyness et al., 2007) demonstrating a preponderance of similarities in variables associated with three different criteria for SSD. Our review did not include data on early or middle adulthood SubD, limiting extrapolation of findings to other age groups.

As psychiatry moves toward DSM-V, establishing consensus on terminology, definitions and criteria for SubD should be an important goal. This will allow for creating an agenda on future SubD research. Priority areas should include studies of incidence, prevalence, and longitudinal course of SubD in various clinical settings, diverse geographical areas, and cultural/socioeconomic groups. While some late-life SubD risk factors (e.g., female gender, medical illness, functional disability, and poor social support) seem well established, others remain to be identified, in order to guide effective prevention efforts (Reynolds, 2008). More sophisticated health economic studies of the effects of SubD would assist in formulating optimal healthcare policy. Based on existing literature, there is certainly evidence to make a case for developing interventions targeted at prevention of SubD (van't Veer-Tazelaar et al., 2009; Vahia et al., 2010). This could potentially be a simple and low-cost means of reducing global morbidity and mortality among older adults.

It would be important to ascertain whether late-life SubD is associated with other forms of psychopathology as a risk factor, consequence, or comorbidity. Existing studies suggest that SubD is associated with both threshold and subthreshold anxiety disorders (Kvaal et al., 2008; Palmer et al., 1997) in older adults—Geisselmann et al. (2001) reported that 32% of

older adults with SSD experienced significant anxiety symptoms (though not specifically DSM disorders). SubD is also prevalent among older persons with schizophrenia (Zisook et al., 2007; Diwan et al., 2007). While a comprehensive review of comorbidity of SubD and subsyndromal anxiety or other psychiatric conditions is beyond the scope of this work, we believe that an exploration of the course of illness and outcomes associated with psychiatric comorbidity is warranted. Depressive symptoms have also been associated with higher cardiovascular and cerebrovascular morbidity, as well as higher mortality in the elderly. These associations may have plausible biological underpinnings that merit further research (Schulz et al., 2000; Schulz et al., 2009).

As SubD becomes a focus of increased research, our understanding of the continuum of mood pathology from “normal” to major depression will be enhanced. Based on existing research, a need to clarify the terminology associated with subsyndromal forms of depression is clear. This will be an important step in facilitating more valid and reliable research in this area. Finally, research advances in understanding the neurobiology of late-life SubD and development of psychosocial and pharmacological treatments are necessary to guide evidence-based treatment algorithms. Such advances could save millions of older adults from the morbidity associated with depressive symptoms that, in spite of their notable prevalence and impact, are often overlooked, under-diagnosed, and under-treated.

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Figure 1.
PubMed Search Results

Table 1

Epidemiological Studies of Subthreshold Depression in Older Adults

Study	Sample Description (n)	Definition of SSD	Results	Comments
(A) COMMUNITY-BASED				
Blazer and Williams (1980)	Community-dwelling (US), age ≥ 65 (n=997)	Older American Resources and Services (OARS) Depression Scale: "dysphoria" = + on ≥ 4 of 7 items; depressive disorder = ≥ 4 depressive criteria symptoms on an 11 item scale that assessed MDD symptoms (sxs) (except suicidality)	<u>Point prevalence</u> Total depressive symptoms: 14.7% <ul style="list-style-type: none"> 4.5% dysphoria without DSM-III mood disorder 6.5% "medically related" depressive symptoms 1.8% primary MDD 1.9% depressive disorder comorbid with cognitive or thought disorder SubD:SD = 2.5:1 Female:male [†] = 2.2:1	One of the original studies to examine depressive symptoms out of the context of DSM disorders; no formal criteria for SubD diagnosis; current studies less likely to try to establish "medical etiologies" of depressive symptoms, i.e. to use an inclusive diagnostic approach.
Beekman et al. (1995)	CD (Netherlands), age 55–85 (n=3056)	DIS DSM-III MDD criteria MinD= CESD ≥ 16 but not meeting MDD criteria	<u>1-month prevalence</u> MDD: 2.02% MinD: 12.9% MinD:MDD = 6.4:1 Female:male = 1.6:1	MinD not defined by usual criteria (more akin to definitions used for SSD); still generally close to most CD estimates; advantage of large sample size
Judd and Kunovac (1998)	CD (US) age ≥ 65 (n=10,256), data from 3/5 ECA study sites	DSM-IV MinD, MDD, DYS SSD: Judd et al. criteria**	<u>1 month prevalence</u> MDD: 6.3% Dysthymia: 8.1% MinD: 13.0% \SubD: 31.1% SSD: 18.1% [†] SubD:MDD = 4.9:1 No separate gender data reported for each diagnosis	Relatively high estimates of SubD but is a one-month estimate with perhaps more inclusive definition of SSD also combined with MinD for our estimate; large sample size using secondary data analysis
Newman et al. (1998)	CD (Canada) age ≥ 65 (n=119)	GMS-AGECAT diagnosed MDD and MinD versus DSM-IV diagnosed MDD and MinD	<u>Point prevalence</u> GMS-AGECAT diagnosis MinD: 9.0% MDD: 2.3% MinD:MDD = 3.9:1 DSM-IV diagnosis MDD: 3.6% MinD: 0.86% MinD:MDD = 4.2:1 No separate gender data reported for each diagnosis	Comparison of two diagnostic systems; GMS-AGECAT more commonly used outside the US; this system yielded notably higher prevalence rates than DSM-IV criteria; GMS-AGECAT diagnoses were primarily driven by dysphoric symptoms; ratios of MinD:MDD similar between two diagnostic methods
Paivarinta et al. (1999)	CD (87%) + LTC (13%) (Finland) age ≥ 85 (n=339)	"clinical interview" for DSM-III-R MDD and MinD (2–4 symptoms)	<u>Point prevalence</u> MDD: 5.6% MinD: 18.6% MinD:MDD = 3.3:1 Female:male = 1.02:1	Study specifically focusing on the "old-old" without dementia (mean age 87.6); MinD was associated in linear regression with poor physical health and ambulatory disability; Inclusion of small minority of persons in institutions may have elevated prevalence rates
Geiselmann and Bauer (2000)	CD AND LTC (Germany) age	GMS and psychiatrist	<u>Point prevalence</u> MDD: 4.5%	Another different criteria for SubD but probably captured

Study	Sample Description (n)	Definition of SSD	Results	Comments
	70–100 (n=516)	diagnosis <ul style="list-style-type: none"> MDD/DYS: DSM-III-R SubD= DSM-III-R Depression NOS "Depressive symptoms" = above GMS depression scale threshold + depressed mood and/or anhedonia 	DYS: 2.1% SubD: 17.8% Depressive sxs: 8.3% SubD:MDD = 4.0:1 No separate gender data reported for each diagnosis	both more traditionally defined MinD and SSD, leading to higher prevalence estimate; Proportion of subjects who were CD vs. in LTC was not reported, complicating interpretation and likely elevating rates above a pure CD study
Heun et al. (2000)	CD (Germany) age ≥60 (n=287)	Composite International Diagnostic Interview (CIDI) for DSM-III-R criteria for MinD, Recurrent Brief Depression (RBD), and MDD	<u>Point Prevalence</u> MDD: 3.5% DYS: 0.7% MinD: 0% \ SubD: 8.4% RBD: 8.4% ↗ RBD: MDD = 2.4:1 <u>Lifetime Prevalence</u> MDD: 4.9% DYS: 5.6% MinD: 23% \ SubD: 35.6% RBD: 12.6% ↗ SubD:MDD = 7.3:1 Female:male = 1.5:1	Difficult to reconcile the point prevalence of 0% for MinD in contrast to the lifetime prevalence of 23% for the same disorder; one of few studies to examine lifetime prevalence, with a notably high ratio of SubD:MDD; relatively smaller sample size
Geiselmann et al. (2001)	CD (Germany), age 70–100 (n=516)	SSD: GMS + for depressive symptoms followed by psychiatrist interview determining significant mood disorder not meeting any DSM-III-R criteria	<u>1-month prevalence</u> MDD: 4.5% SSD: 16.5% SSD: MDD = 3.7:1 Female:male = (young-old) 1.6:1 Female:male = (old-old) 1:1	Higher end of SSD prevalence partially accounted by 1-month prevalence; ratio SSD:MDD close to average; lowering of female:male gender of SubD diagnosis possibly continues with increasing age.
Hybels et al. (2001)	CD (US) age ≥65 (n=3996)	Modified version of CESD: "Syndromal Depression" (SD) score >9 SSD score 6–8	<u>Point prevalence</u> SD 9.1% SSD 9.9% SSD: SD = 1.1:1 Female:male = 1.3:1	Use of "modified" scale to classify diagnosis is a limitation; overall SSD prevalence similar to other reports but "SD" prevalence higher than usual reports of CD late-life MDD. This may have classified some persons with MinD or SSD in SD, underestimating SubD prevalence.
Murphy et al. (2002)	CD (Canada) mixed adult age groups with mean age = 63 (n=489)	Diagnostic Interview Schedule for DSM-III MinD: DSM criteria but allowed some who failed criteria for symptom severity or symptom clustering SSD: ≥ 2 depressive symptoms but not endorsing 2 weeks of dysphoria	<u>Point Prevalence</u> MDD: 3.3% MinD: 10.8% \ SubD 22.9% SSD: 12.1% ↗ SubD:MDD = 6.9:1 <u>No separate gender data reported for each diagnosis</u>	Modified criteria for both MinD and SSD not matching any other criteria precisely limit interpretation and synthesis, perhaps also leading to elevated prevalence estimates
Østbye et al. (2005)	CD (Canada), age ≥65 (n=1659)	"12-item rating scale" to diagnose MDD (5–9 symptoms for ≥2 weeks) and MinD (2–4 sxs for ≥2 weeks) according to DSM-III-R	<u>Point prevalence</u> MDD: 2.2% MinD: 4% MinD:MDD = 1.8:1 Female (vs. male) gender increased odds ratio (OR 4.7) for MinD in regression	One of the few community studies to assess only MinD (versus SSD) according to stricter DSM criteria, yielding lower prevalence estimates of this form of SubD; same study also

Study	Sample Description (n)	Definition of SSD	Results	Comments
			Analysis	separately assessed epidemiology in LTC (reported below)
Cohen et al. (2005)	CD (US) age ≥55, (n=860 blacks [B], 214 whites [W]), total n=1074	SD: CES-D ≥ 16 SSD: CES-D 8–15	<u>Point prevalence</u> SD (B) 8% SD (W) 10% SD (total) 8.4% SSD (B) 13% SSD (W) 28% SSD (total) 16% SSD: SD (B) = 1.6:1 SSD: SD (W) = 2.8:1 SSD: SD (total) = 1.9:1 For blacks, female gender was significant predictor of SSD (OR 1.9), much less than for SD; female gender not associated with SSD in whites	The differences in prevalence between blacks and whites were largely accounted for by high rates in Caribbean-American blacks; American-born blacks were more similar to whites; use of symptom scale to classify SSD rather than diagnostic criteria is a limitation.
Schoevers et al. (2006)	CD (Netherlands) age ≥65, (n=4051)	GMS-AGECAT score 1–2 for SSD, 3–5 for SD	<u>Point prevalence</u> SD: 12.9% SSD: 21.3% SSD: SD = 1.7:1 Female sex accounted for 10.8% of the attributable risk of subsequent late-life MDD risk	Relatively higher absolute rates than seen in most studies though SSD:SD ratio again lower than average—similar to above study that used GMS and AGECAT for diagnosis
Chen et al. (2007)	CD (Taiwan) age ≥65, (n=1500)	GMS for MDD or SSD as defined by Lavretsky and Kumar (Lavretsky and Kumar, 2002): depressed mood or anhedonia + ≥2 depressive symptoms + HAM-D ≥10 (or GDS ≥12) + distress/impairment for ≥1 month duration	<u>1-month prevalence</u> MDD: 3.3% SSD: 8.8% SSD: MDD = 2.7:1 Female:male = 2.4:1	Only study to use Lavretsky and Kumar criteria in this review; 1 month prevalence but similar to findings from other CD studies, in part validating their criteria
Chuan et al. (2008)	CD (Singapore), age ≥60 (n=1028)	GMS-AGECAT score 1–2 for SSD, 3–5 for syndromal depression (SD)	<u>Point prevalence</u> SD 5.5% SSD 9.6% SSD: SD ratio = 1.7:1 Female:male = 1.3:1	GMS and AGECAT unfamiliar tools for many in US; unclear how this maps onto DSM diagnoses; SSD:SD and female:male ratios lower than several other CD studies
Kvaal et al. (2008)	CD+LTC (UK) age ≥65, (n=2535)	GMS-AGECAT score 1–2 for SSD, 3–5 for syndromal depression (SD)	<u>Point prevalence</u> SD: 14% SSD: 25% SSD: SD = 1.8:1 Increased OR (2.5) for females to have SubD	GMS and AGECAT unfamiliar tools for many in US; unclear how this maps onto DSM diagnoses; Proportion of subjects who were CD vs. in LTC was not reported, complicating interpretation and likely elevating rates above a pure CD study
Maercker et al. (2008)	CD (Switzerland) age ≥65, (n=570)	CES-D items transformed into diagnostic criteria for MDD and RBD; SSD defined as CES-D ≥16 but not meeting criteria for MDD or RBD	<u>Point prevalence</u> MDD: 2.3% RBD: 3.0% & SubD: 9.3% SSD: 6.3% SubD: MDD = 4:1 Female:male = 1.9:1	Symptom scale rather than diagnostic criteria used; SubD:MDD and female:male ratios similar to average findings

Study	Sample Description (n)	Definition of SSD	Results	Comments
Preville et al. (2008)	CD (Quebec, Canada) Age ≥ 65 (n=2798)	In-person interviews in French with ESA-Q (<i>Enquête sur la Santé des Aînés</i> -Diagnostic Questionnaire); MDD standard DSM-IV definition; MinD similar criteria but only 2–4 symptoms	<u>12-month prevalence</u> MinD: 5.7% MDD: 1.1% MinD:MDD = 5.2:1 Female:male= 1.8:1	Absolute rates low for 12-month prevalence but only MinD included; Ratio on MinD:MDD still close to other reports; female:male ratio in MinD similar to generally cited 2:1 ratio in MDD
Steffens et al. (2009)	CD (87%) + LTC (13%) (US) Age ≥ 70 (n=851)	Interpretation of previously obtained CIDI-SF applying DSM-IV concepts of MDD and MinD (90.5% of participants) if deemed cognitively intact or simply categorized as “depressed” based on limited data from NPI for cognitively impaired	<u>12-month prevalence (not prospectively measured, but rather as per participant recall of symptoms):</u> MDD: 1.6% MinD: 1.4% MinD:MDD = 0.83 Female:male $\approx$ 1:1 <u>Also included in depression prevalence anyone on antidepressant, yielding total prevalence, including MDD, MinD, and antidepressant users of 11.2%</u>	Recall bias makes 12-month prevalence estimates less accurate than prospective studies; somewhat unorthodox methods of diagnostic ascertainment may explain estimates that are incongruent with most epidemiological studies (until they add in users of antidepressants, a method of diagnosis not used in any other study to our knowledge); data for CD vs LTC could not be separated; NPI depression diagnosis was not methodologically sound
Vahia et al. (2010)	CD (US) Women Age ≥ 60 (n=1979)	SSD defined as CES-D 8–15 SD defined as CES-D ≥ 16	<u>Point prevalence</u> SSD: 20.2% SD: 7% SSD:SD = 2.9:1 All subjects were females	Limitations of purely symptom scale-based depression categorization; exclusively female participants likely to elevate prevalence rates
(B) PRIMAR Y CARE-BASED				
Williams et al. (1995)	PCP (US), mean age 60; 53% Mexican American (n=221)	SCID for DSM-III to diagnose MDD SSD = depressed mood +/- anhedonia and 1–3 other DSM-III depressive symptoms	<u>Point prevalence</u> MDD: 4% SSD: 16% SSD: MDD = 4:1 No separate gender data reported for each diagnosis	SSD definition virtually identical to criteria for MinD though not named as such; large Latino minority population; captures a “young-old” sample; 11% of interviews done in Spanish
Lyness et al. (1999)	PCP (US), age ≥ 60 (n=224)	SCID for DSM-III-R MDD or MinD SSD HAM-D > 10 but not meeting criteria for MDD or MinD	<u>Point prevalence</u> MDD 6.5% MinD 5.2%\SubD 15.1% SSD 9.9% SubD:MDD = 2.32:1 No separate gender data reported for each diagnosis	SSD defined by symptom scale rather than criteria (although later study by same author showed little difference in associated variables when defined this way versus other criteria)
Aranda et al. (2001)	PCP (US) mean age 69.3, all Latinos	Patient Health Questionnaire (PHQ) defined MDD or SubD (details not clearly specified)	<u>Point prevalence</u> MDD: 4% SubD: 20.1% SubD:MDD = 5.0 Gender was not predictive of depression diagnosis	Methods of transforming PHQ scores to diagnosis through computer algorithm not explicitly described; not necessarily representative of Latinos in general (English-speaking, urban, mostly Mexican-American); no measure of acculturation but being US-born borderline predictive of depression (p=0.07)

Study	Sample Description (n)	Definition of SSD	Results	Comments
Berradi et al. (2002)	PCP (Italy) age ≥60 (n=606)	WHO ICD Checklist for Depression: current depressive episode (CDE) =4+ symptoms; SSD = anhedonia and/or depressed mood for 2 weeks but not CD episode	<u>Point prevalence</u> CDE 8.6% SSD 3.6% SSD:CD = 0.52:1 Female:male = 2.8:1	Ratio of SubD:MDD reversed from virtually every other study; possibly secondary to ICD definition of current depressive episode versus MDD, yielding higher rates of CD than US estimates of MDD in primary care
Licht-Strunk et al. (2005)	PCP (Netherlands) age ≥55 (n=986)	PRIME-MD used to define MDD according to DSM-IV MinD defined as GDS(s) ≥5 but no MDD; used subsample persons with GDS(s) < 5 interviewed for MDD to impute additional MDD prevalence	<u>Point prevalence</u> MDD: 13.7% (<i>imputed</i>) MinD: 10.2% MinD:MDD = 0.74:1 MDD: 8.8% (<i>non-imputed</i>) MinD: 10.2% MinD: MDD = 1.2:1 Female:male = 1.04	Definition of MinD does not allow for imputation of prevalence not detected on symptom measure screening instrument as was done for MDD, thus confounding assessment of relative prevalence of MinD and MDD; non-traditional criteria for MinD used
Lyness et al. (2007)	PCP (US), age ≥65 (n=662)	SCID DSM IV MDD or MinD SSD-A: HAM-D > 10 but no MDD/MinD SSD-B: Judd et al. Criteria** SSD-C: Lyness et al. Criteria*	<u>Point prevalence</u> MDD 4.2%; MinD 6.3%; SSD-A 20.4% SSD-B 16.2% mean: 21.6% SSD-C 28.1% Females: males = (A) 2.56:1; (B) 2.06:1; (C) 2.21:1 (MEAN): 2.3:1 SubD (A): MDD = 6.36:1 SubD (B): MDD = 5.36:1 SubD (C): MDD = 8.19:1 SubD (mean): MDD = 6.6:1	Nice demonstration that even though definitions of SubD have varied, many are measuring similar concepts, i.e. prevalent mood illnesses with significant morbidity; SSD-B most restrictive vs. SSD-C least restrictive definition
Lyness et al. (2009)	Primary care patients (PCP) (US), age ≥65 (n=484)	SCID DSM IV diagnosis for MDD, MinD, and DYS; Lyness et al. criteria* for SSD	<u>Point prevalence</u> MDD 4.8% SubD 35.9% SubD:MDD = 7.5:1 Female:male = 2.1:1	Study is unique in that it included DSM DYS in SubD group without a break-down of relative proportions of DYS, MinD, and SSD, perhaps contributing to higher SubD:MDD ratio
(C) MEDICAL INPATIENTS				
Koenig et al. (1991)	Medical inpatients (US) age ≥70, all males in VA hospital (n=332)	Diagnostic Interview Schedule for DSM MDD or MinD	<u>Point prevalence</u> MDD 13.3% MinD 29.2% MinD:MDD = 2.2:1 All subjects were males	Unique all male veteran population makes it more difficult to extrapolate results; rates were also calculated among inpatients <40 yo in which MDD was more common than MinD (reverse pattern) in ratio 1.24:1
Koenig et al. (1997)	Medical inpatients (US), age ≥60 (n=542)	MinD = anhedonia or depressed mood + 1–3 other depressive symptoms OR ≥3 depressive symptoms in the absence of depressed mood and anhedonia	<u>Point prevalence</u> MDD 21.6% MinD 27.9% MinD:MDD = 1.3:1 MinD not associated with female gender	Of the medical inpatient studies of SubD, perhaps the best methods; definition of MinD veered from pure DSM definition and included some who would be classified as SSD by some proposed criteria
Schneider et al. (2000)	Medical inpatients (Germany), age ≥60 yo (n=262)	Psychiatrist interview with ICD-10 checklist and Impairment Scores (≥5 = MDD, 3–4 = SSD); subsequent	<u>Point Prevalence</u> “Inclusive approach”: MD 35.5%, SSD 32.1% “Exclusive approach” examining for organic causes:	Diagnosis according to “impairment scores” seems unorthodox given many other ways to diagnose the disorders; becoming less common to attempt to deem

Study	Sample Description (n)	Definition of SSD	Results	Comments
		evaluation for symptoms deemed to be “organic” in origin	MD 14.1% SSD 17.6% “organic” mood disorders 12.2% SSD:MDD (<i>exclusive</i>) = 1.3:1 Female:male = 1.9:1	a sizable portion of depression diagnoses as “organic” due to unreliability and favoring of inclusive diagnostic approach; Either way (inclusive or exclusive) SSD and MDD had similar relative prevalences
McCusker et al. (2005)	Medical inpatients (Canada, 2 hospitals), age ≥65 yo (n=380)	DIS DSM-IV MDD and MinD	<u>Point prevalence</u> MDD (Hospital A) 14.2% MDD (Hospital B) 44.5% MinD (Hospital A) 9.4% MinD (Hospital B) 7.9% Sample sizes were not reported for Hospital A versus B, preventing average prevalences of depressive disorders or their relative prevalence Female gender not associated with depressive disorder diagnoses	Wide variability in MDD prevalence between sites calls study findings and methodology into question; in both settings, MDD was more common than MinD, a reversal of findings from CD and PCP based studies
(D) LONG-TERM CARE SETTINGS				
Parmelee et al. (1989)	LTC (US) mean age 84 (n=708)	MDD: DSM-III-R or GDS >17 then consensus diagnosis MinD: DSM-III-R or GDS 11–17 then consensus diagnosis	<u>Point prevalence</u> MDD 12.4% MinD 30.5% MinD:MDD = 2.5:1 No separate gender data reported for each diagnosis	Relatively better standards for making diagnoses, yielding results not unlike other LTC studies, although again not evaluating SSD likely lowers total SubD prevalence
Rovner et al. (1991)	LTC (US), mean age c. 81 (n=454)	Screened by psychiatrist with Modified Present State Exam for depressive disorder according to DSM-III-R and “depressive symptoms” (depressed mood but no DSM-III-R mood disorder)	<u>Point prevalence</u> MDD: 12.6% “depressive symptoms”: 18.1% SubD:MDD = 1.4:1 No separate gender data reported for each diagnosis	Rate of MDD similar to two subsequent LTC studies but classification of SubD somewhat lacking in sophistication
Parmelee et al. (1992)	LTC and congregate apartments (US); mean age 83.9 (n=868)	Schedule for Affective Disorders (SADS) + GDS: MDD = dysphoria (on SADS or GDS ≥11) and 4 other depressive symptoms; MinD = dysphoria (on SADS or GDS ≥11) but not meeting MDD criteria	<u>Point prevalence</u> MDD total 15.7% • LTC 24.6% • apartments 10% MinD total 16.5% • LTC 20.2% • apartments 14.1% MinD:MDD (LTC) = 0.82:1 MinD:MDD (apmts) = 1.4:1 No separate gender data reported for each diagnosis	Mixed settings of LTC and “congregate apartments” likely what would be called assisted or independent living; high rates of MDD in NH and slightly higher rates of MinD in apartments; definition of MinD not as standardized as later studies and no inclusion of SSD likely lowers overall SubD rates
Teresi et al.(2001)	LTC (US) mean age 84.5; 82% female (n=319); included many cognitively impaired	DSM-III-R criteria for “probable/definite” MDD; RDC for MinD; SSD = SelfCARE depression score >7 or “possible” MDD or MinD	<u>Point prevalence</u> MDD 14.4% MinD 16.8% \SubD 60.8% SSD 44% ✓ SubD:MDD = 4.2 No separate gender data reported for each diagnosis	Even higher rates of mood disorders than Jongenelis et al., perhaps influenced by high rate of cognitive disorders; again SSD defined only by symptom scale is a limitation and terminology “possible”

Study	Sample Description (n)	Definition of SSD	Results	Comments
	subjects			MDD/MinD not standard diagnoses.
Jongenelis et al. (2004)	LTC residents (Netherlands) mean age 79.3; 69% female (n=333)	MinD and MDD diagnosed according to DSM-IV criteria using WHO Schedules for Clinical Assessment in Neuropsychiatry (SCAN); SSD = GDS >10 but no DSM-IV mood disorder	<u>Point prevalence</u> MDD 8.1% MinD 14.1% \SubD 38.1% SSD 24% $\nearrow$ SubD:MDD = 4.7:1 Gender not associated with depression risk	Substantially higher rates of all mood disorders in institutional settings; limitation of SSD defined by symptom scale rather than diagnostic criteria.
Østbye et al. (2005)	LTC (Canada), age ≥ 65 (n=1255)	"12-item rating scale" to diagnose MDD (5–9 symptoms for ≥ 2 weeks) and MinD (2–4 sxs for ≥ 2 weeks) according To DSM-III-R	<u>Point prevalence</u> MDD: 7.7% MinD: 4% MinD:MDD = 0.52:1 Female gender increased odds ratio for MinD in regression analysis	Notably lower estimates of MinD versus other LTC studies despite similar criteria; same study also separately assessed epidemiology in community (reported above) and was not thus specifically designed to assess depression in LTC alone
Morrow-Howell et al. (2008)	LTC (US) mean age 72; 77% female; 28% African-American (n=1170)	DIS for DSM IV MDD/DYS: SubD: modified CESD ≥ 9 but no MDD/DYS	<u>Point prevalence:</u> MDD: 6% DYS: 0.5% SubD: 19.1% SubD:MDD = 3.2:1 No separate gender data reported for each diagnosis	Lower rate of SubD than in other LTC studies may relate to lack of MinD/SSD specific criteria and/or the fact that assessments were conducted on admission to LTC

* ≥ 2 depression symptoms, at subthreshold or threshold level, with at least one being depressed mood or anhedonia, not meeting criteria for MDD, MinD, or DYS

** ≥ 2 depression symptoms at threshold level for ≥ 2 weeks, not meeting criteria for MDD, MinD, or DYS

$\nearrow$ When possible, gender ratios within the SubD group or data related to gender are included

AGECAT (Automated Geriatric Examination for Computer-assisted Autonomy); CD (community-dwelling); CES-D (Center for Epidemiological Studies Scale for Depression); CIDI-SF (Composite International Diagnostic Interview-Short Form); DIS (Diagnostic Interview Schedule); DSM (Diagnostic and Statistical Manual for Mental Disorders); DYS (dysthymia); ECA (Epidemiological Catchment Area study); GDS (Geriatric Depression Scale); GDS(s) (Geriatric Depression Scale-short form); GMS (Geriatric Mental State Exam); HAM-D (Hamilton Rating Scale for Depression); ICD (International Classification of Disease); LTC (long term care); MDD (major depressive disorder); MinD (minor depression); NH (nursing home); NPI (Neuropsychiatric Inventory); PCP (primary care patients); PRIME-MD (Primary Care Evaluation of Mental Disorders) RBD (recurrent brief depression); RDC (Research Diagnostic Criteria); SCID (Standardized Clinical Interview for DSM); SD (syndromal depression); SSD (subsyndromal depression); SubD (subthreshold depression); VA (Veterans Affairs); WHO (World Health Organization)