Definition of Subsyndromal Depression in Late Life

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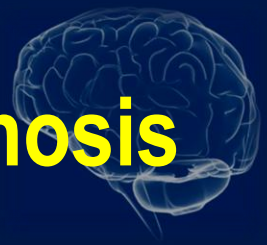
Late life depression

- Major factor causing severe health problems
  - Associated with increased morbidity, mortality, medical illness and dementia
  - 4th cause of Disability Adjusted Life Years (DALY)s in 1990 (Murray, 1997)
  - 3th cause of DALYs in high-income countries and & 7th cause of DALYs in low-income countries (Lopez, 2006)

- But underrecognized and undertreated
  - Sub-syndromal feature of LLD
  - Complicated etiologies
  - Being mistaken as problems of aging

Diagnostic Problem in Depression Diagnosis



- Changes in clinical presentation and severity of depression are frequently encountered over time.

- Unipolar depressive disorder is a pleomorphic mood disorder **(1996 CINP President's Workshop conclusion)**
  - consisting of a cluster of depressive subtypes existing in a relatively homogeneous, symptomatic clinical continuum

- The most striking feature of depression in primary care is the prominence of clinically meaningful depressive symptoms that do not meet criteria for major depressive disorder

Depressive disorders

Severity of depressive disorders

No Depression	Non-major depression	Major Depressive Disorder

Impact of depressive disorders

Prevalence rate of depressive disorders

Non-Major depression

- Too minor to qualify for diagnosis of major depression
- Terms such as "*minor, subsyndromal, or subthreshold depression"*
- Higher prevalence than major depression
- Cause the same poor outcome as major depression
  (Judd et al., 1996; Lyness et al, 1999; Chen et al., 2000; Beekman et al.,2002)
- Non-Major depression
  - Minor depressive disorder (MnDD) in Appendix B of the DSM-IV
  - Subsyndromal depression (SSD)
  - Depression symptoms case defined by depression scales

Subsyndromal depression

- No agreement upon “gold standard”
- Clinical significance
  - Adverse clinical outcomes
    (Wells et al., 1989; Broadhead et al., 1990; Judd et al.,, 2000)
  - Increased social dysfunction and disability
    (Lyness,1999; Lavretsky, 2002)
  - Increased risk for future mood disorders (Judd et al, 1997)
  - Increased uses of medical and mental health services in the elderly (Johnson, 1992; Wagner, 2000)
- Commonly defined dimensionally using a cutoff scores of depression rating scales

Prevalence of depressive symptoms case defined by CES-D

Investigator	Year	Country	N	Age (yrs)	Instrument	Criteria	Prevalence (%)
Western countries							
Blazer	1991	USA	3,998	≥65	CES-D	≥16	9.0
Fuhrer	1992	France	2,792	≥65	CES-D	≥16	13.6
Madianos	1992	Greece	251	≥65	CES-D	≥16	27.1
Beekman	1995	Netherlands	3,056	55-85	CES-D	≥16	14.9
Bassuk	1998	USA	2,812	≥65	CES-D	≥16	15.0
Minicuci	2002	Italy	2,398	≥65	CES-D	≥16	49.0
Zunzunegui	1998	Spain	1,116	≥65	CES-D	≥16	37.0
Hybels	2001	USA	3,996	≥65	CES-D	≥16	9.1
Eastern countries							
Kim	unpubished	Republic of Korea	714	≥65	CES-D	≥16	28.8
Ihara	1993	Japan	695	≥65	CES-D	≥16	5.3

Prevalence of depressive symptoms case defined by GDS/Short form GDS

Investigator	Year	Country	N	Age (yrs)	Instrument	Criteria	Prevalence (%)
Eastern Countries							
Woo	1994	Hong kong	1,611	≥70	GDS	≥16	35.0
Kim JM	2002	Republic of Korea	1,134	≥65	GDS	≥19	33.0
Ganatra	2008	Pakistan	402	≥65	Short form-GDS	≥5	22.9
Cheng	1997	China	1,997	≥65	Short form-GDS	≥8	26.0
Liu	1997	China	1,313	≥65	Short form-GDS	≥5	25.7
Wada	2004	Japan	5,363	≥65	Short form-GDS	≥6	33.5
Chi	2005	Hong Kong	917	≥60	Short form-GDS	≥8	12.5
Wada	2005	Japan	1,905	≥60	Short form-GDS	≥6	30.3
		Indonesia	411	≥60	Short form-GDS	≥6	33.8
		Vietnam	379	≥60	Short form-GDS	≥6	17.2
Lee	2005	Republic of Korea	1,587	≥65	Short form-GDS	≥8	15.2
		Japan	1,650	≥65	Short form-GDS	≥6	19.8
Kim KW	2006	Republic of Korea	714	≥65	Short form-GDS	≥8	31.6
Kim KW	2008	Republic of Korea	6,141	≥65	Short form-GDS	≥8	27.7
Kim KW	2008	Republic of Korea	6,141	≥65	Short form-GDS	≥6	39.5
Western countries							
Papdopoulos	2005	Greece	965	≥60	Short form-GDS	≥7	27
Romero	2005	USA	798	≥65	Short form-GDS	≥5	5.4 -19.2
Garcia-Pena	2008	Mexico	7,449	≥60	GDS	≥11	21.7

Wide variation of Prevalence of Depressive symptoms case

- Case defined by CES-D≥16
  - **Very different between countries (**5.3% to 49.0%)
  - High in Italy, Spain, Korea, and Greece
  - Low in Japan and USA
- Case defined by GDS
  - **Different between countries (**12.5% to 49.6%)
  - but the difference was lower than case defined by CES-D≥16

➔ Wide Variation

➔ Over-inclusive (up to nearly 50%)

➔ Different cutoff point in GDS

Comparison of the prevalence of depressive symptoms case in Eastern countries

- Korea > China > Japan
- High prevalence in Korean
  - Cutoff point of CES-D(15/16)
    - 28.8% in Korea vs. 5.3% in Japan
  - Cutoff point of GDS(15/16)
    - 49.6% in Korea vs. 35% in Hong kong
  - Cutoff point of short form GDS(5/6)
    - 39.5% in Korea vs. 19.8%~33.5% in Japan
  - Cutoff point of short form GDS(7/8)
    - 27.7% in Korean vs. 26.0% in China
- Difference of prevalence
  - Despite similar cultural backgrounds of Eastern Countries, the prevalence rates were different
  - Decreased if case was defined by GDS cutoff point

Cross-Cultural Comparability of Non-Major Depression

- Methodological challenge in cross-cultural research
  - Diversity in pattern of presenting depressive moods according to racial and ethnic diversity (Blazer et al., 1998)
  - The scores of depression scale are very different across cultural backgrounds
    - Reluctant to respond positively to positive affect questions in Eastern countries (Iwata, 1989; Cho and Kim, 1998, *Noh et al.,1992; Noh and Chen, 1998*)
    - To report symptoms of distress more openly and directly in Korean Elders
  - It is not appropriate to compare the prevalence of the non-major depression between countries using depression scales such as CES-D and GDS
  - Equivalence of measurement is needed across different cultural samples

Categorical Approach in Subsyndromal Depression

- Standard diagnostic criteria of Subsyndromal Depression is a prerequisite for cross-cultural comparative studies
  - Categorical approach similar to DSM criteria is needed in the evaluation of Non-Major Depression
- The benefits of categorical approach of clinically significant depression below threshold of MDD
  - Less influenced by cultural backgrounds
  - Evaluated and diagnosed by clinician
  - Enhanced comparability between studies
- Standard categorical diagnostic approach for SSD is needed
  - SSD is generally defined as depression with clinically meaningful depressive symptoms that do not meet criteria for MDD and MnDD

Subsyndromal depression: Problems with Current Research

- No agreement on criteria and definition on subsyndroaml depression
- DSM-IV is not suitable for subsyndroaml depression
- Wide variation of Prevalence rates of Depressive symptoms case defined by depression scales
- No validation study for proposed criteria of subsyndromal depression
- New categorical approach and validation study is required

Prevalence of Subsyndromal depession

Investigator	Year	Country	N	Age (yrs)	Instrument	Criteria	Prevalence (%)
Judd	1994	USA	9,160	General population	DSM-IV	≥2 depressive Symptoms	11.8
Judd	1997	USA	10,526	General population	DSM-IV	≥2 depressive Symptoms	3.9
Goldney	2004	Australia	3,010	General population	DSM-IV	≥2 depressive Symptoms	12.9
Chuan	2008	Singapore	1,092	≥65	GMS-AGECAT		9.6

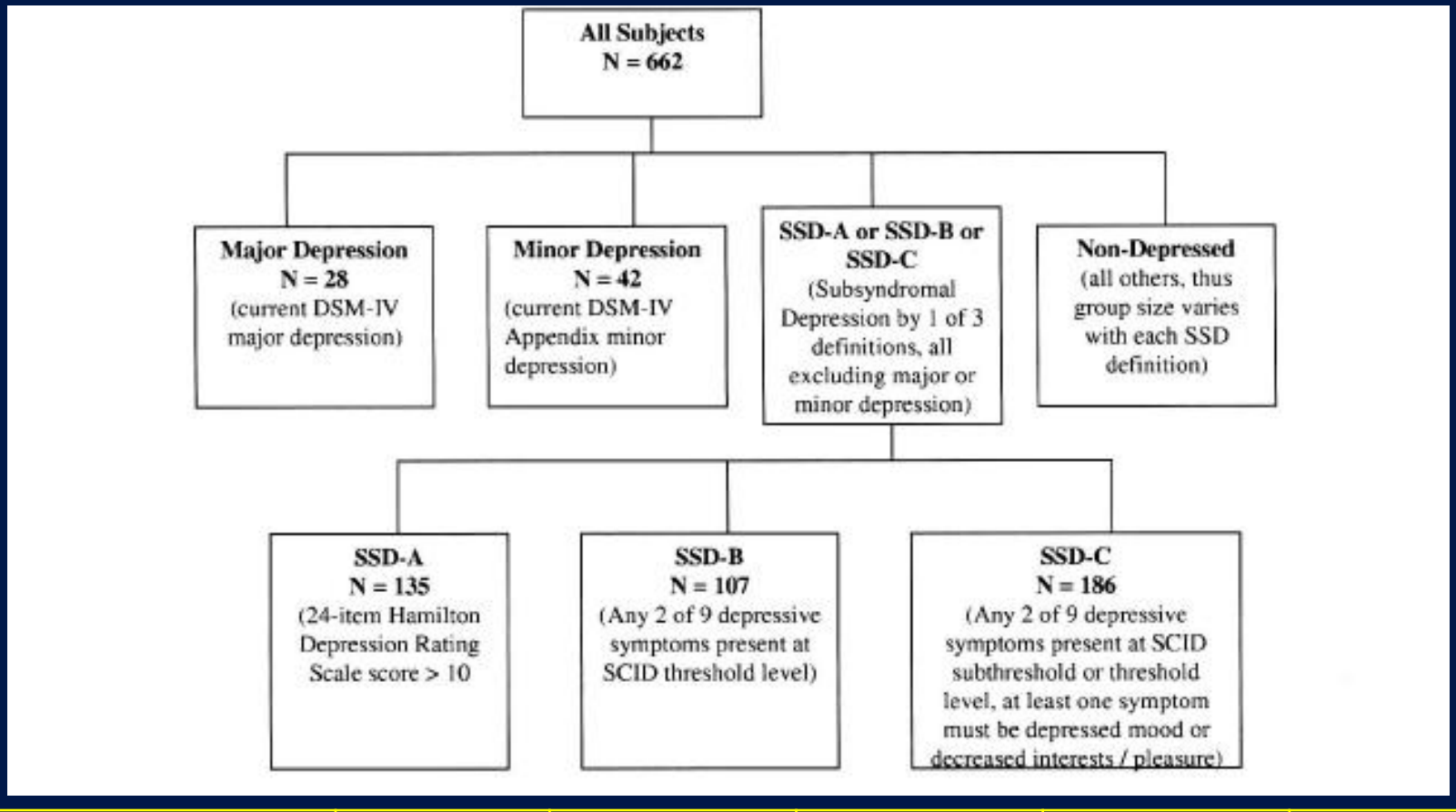
Appropriateness of DSM-IV Diagnostic criteria for subsyndromal depression

- Rigorous DSM diagnostic criteria
  - Widely used in clinical and research setting
  - Most familiar to clinicians and researchers
  - High comparability between studies
- Time threshold of DSM diagnostic criteria
  - "most of day, nearly every day" over a 2–week period
  - Clinically significant depressive symptoms
    - only variably present over the course of each day or week (Chopra, Zubritsky, Knott, *et al*, 2005; Geiselmann & Bauer, 2000)
  - Not suitable for non-major depression
- Modification of DSM-IV diagnostic criteria is required
  - To lower the rigorous time threshold
  - To decrease the number of depressive symptoms

Provisional Dx Criteria of SSD

	SSD-A	SSD-B	SSD-C
No of depressive Sxs	Cutoff scores of depression rating scales	2≥ depressive Sxs	2≥ depressive Sxs
Core depressive Sxs	-	-	At least one core depressive Sxs
Time threshold	-	Most of day and nearly every day over at least 2 weeks	-
Limitation	Over-inclusiveness Large trans-cultural influence	Lack of specificity Strictness of time threshold	To lower a bar of threshold too much
Prevalence rates	5.3%~49.6%	3.9%~12.9%	Not available
Researchers	Beekman, 1995 Chopra, 2005 da Silva Lima, 2007 Lyness, 1999 Snowdon, 1996	Judd, Akiskal, Maser, 1998a Judd, Akiskal, Maser, 1998b Judd, Akiskal & Paulus, 1997 Goldney, 2004	Lyness, 2006; McAvay, 2004

Variation of frequencies of SSD in the same primary care patients according to diagnostic criteria



Depressive disorders	MDD	MnDD	SSD-A	SSD-B	SSD-C
Frequency	4.2%	6.3%	20.4%	16.2%	28.1%

J.M. Lyness et al. Am J Geriatr Psychiatry 15:3, March 2007

Depressive disorders

Severity of depressive disorders

No Depression	Subsyndromal Depression	Minor Depression	Major Depressive Disorder

Impact of depressive disorders

Prevalence rate of depressive disorders

Cutoff point of depressive sx scales	2≥ depressive sx with at least one core sx without time threshold	2≥ depressive sx with time threshold

Operationally defined SSD in KLoSHA

	SSD-B	SSD-C	SSD-KLoSHA
No of depressive Sxs	2≥ depressive Sxs	2≥ depressive Sxs	2≥ depressive Sxs
Core depressive Sxs	-	At least one core depressive Sxs	At least one core depressive Sxs
Time threshold	Most of day and nearly every day over at least 2 weeks	-	more than a half of a day and more than not over at least two weeks
Limitation	Lack of specificity Strictness of time threshold	To lower a bar of threshold too much	
Researchers	Judd, Akiskal, Maser, 1998a Judd, Akiskal, Maser, 1998b Judd, Akiskal & Paulus, 1997 Goldney, 2004	Lyness, 2006; McAvay, 2004	Kim et al , 2006

Clinical Significance of Subsyndromal depression

- High prevalence rate
- Increased Functional Impairments
- Association with Increased Service Utilization & Cost
- Common Neural Substrate with MDD
- Risk for future depression

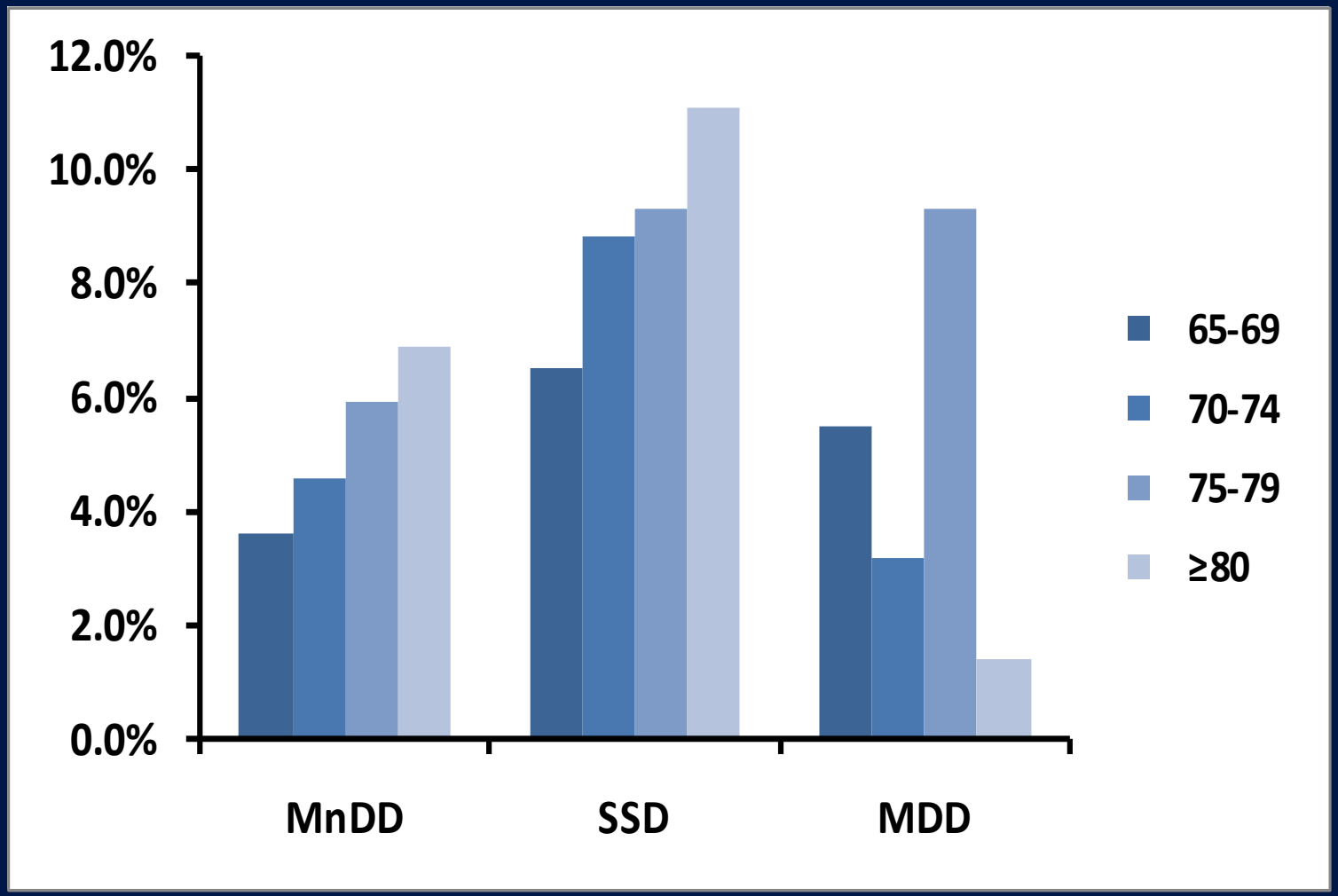
Prevalence rates SSD-K

	MDD	MnDD	SSD- K	CES-D≥16	GDS ≥17
Age (years)					
65-69	5.5 (3.3-8.7)	3.6 (1.8-6.3)	6.5 (4.0-9.9)	22.8 (18.1-27.5)	27.7 (22.7-32.8)
70-74	3.2 (1.3-6.5)	4.6 (2.2-8.3)	8.8 (5.4-13.3)	27.7 (21.7-33.7)	23.8 (18.1-29.5)
75-79	9.3 (4.8-16.1)	5.9 (2.1-11.8)	9.3 (4.8-16.1)	34.5 (25.8-43.1)	32.8 (24.2-41.3)
≥80	1.4 (0.03-7.5)	6.9 (2.3-15.5)	11.1 (4.9-20.7)	35.4 (23.8-47.0)	35.4 (23.8-47.0)
Gender					
Men	2.33 (0.9-4.7)	2.7 (1.2-5.2)	5.0 (2.8-8.1)	17.3 (13.0-21.7)	19.7 (15.2-24.3)
Women	7.02 (4.8-9.9)	6.1 (4.0-8.8)	10.4 (7.6-13.8)	34.7 (30.1-39.4)	34.2 (29.5-38.8)
Age-standardized†	4.91 (3.6-6.8)	4.8 (3.4-6.6)	8.4 (6.5-10.5)	28.2 (24.8-31.5)	28.7 (25.3-32.0)
Age- and gender -standardized†	5.00 (3.6-6.8)	4.8 (3.4-6.6)	8.4 (6.5-10.5)	28.3 (24.9-31.6)	28.9 (25.5-32.3)

*Cases per 100 population of given age with 95% confidence intervals.
† Standardized to 2005 Korean population

Results from KLoSHA

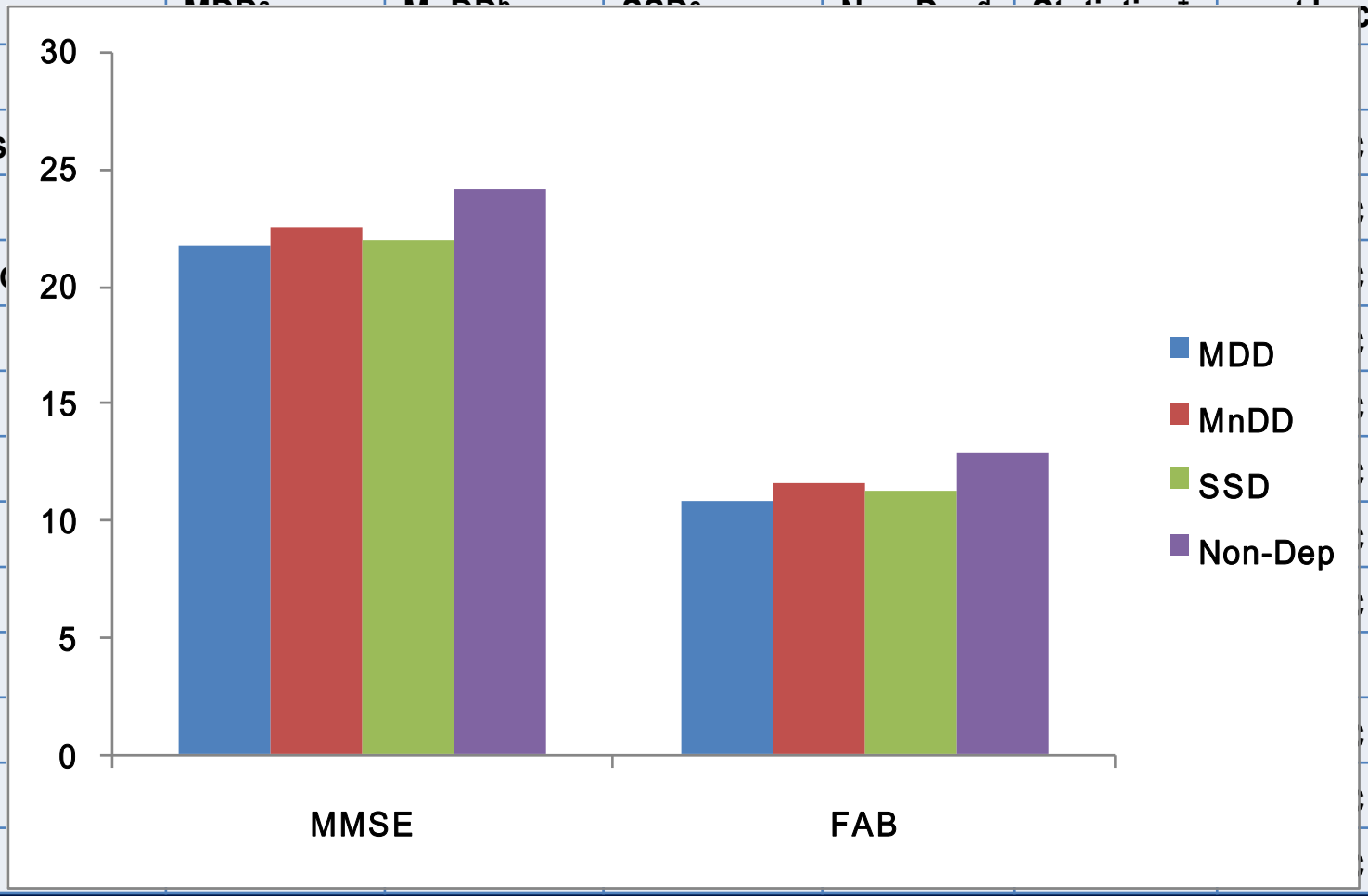
Prevalence rates SSD-K



Results from KLoSHA

Impacts of SSD-K

Number						
Age (years						= d
Education						< d
Gender (w						≠ d
HAM-D						> d
GDS						> d
CES-D						> d
MMSE						< d
FAB						< d
SF-36						
PCS						< d
MCS						< d
CIRS-N						= d



**P<0.001

†F for continuous variables and chi square for categorical variables

‡Bonferroni posthoc comparison for continuous variables and 2X2 chi square test for categorical variables

Results from KLoSHA

Functional Impairments associated with SSD in Late-Life

Clinical Variable	Depression Groups (all values expressed as mean (SD))			
	Nondepressed (n = 162)	Subsyndromal Depression (n = 26)	Minor Depression (n = 13)	Major Depression (n = 23)
Ham-D *	5.1 (2.5)	13.7 (3.1)	14.9 (6.4)	22.6 (6.5)
GAF †	76.5 (12.7)	58.4 (12.8)	59.9 (8.1)	45.3 (9.0)
MMSE ‡	27.6 (2.3)	26.8 (2.3)	26.3 (2.5)	26.4 (3.0)
CIRS §	5.6 (2.9)	7.7 (3.0)	7.4 (3.3)	7.6 (2.7)
KPSS ¶	82.3 (11.3)	71.3 (15.2)	70.3 (19.4)	73.2 (14.3)
IADL ‖	1.6 (3.7)	5.0 (6.0)	6.2 (6.6)	5.7 (6.5)
PSMS #	0.8 (1.8)	1.5 (1.5)	2.3 (2.9)	1.6 (2.0)

*Hamilton Rating Scale for Depression: higher score = greater depressive symptoms.

† Global Assessment of Functioning: lower score = greater functional impairment judged due to psychiatric factors.

‡ Mini-Mental State Examination: lower score = greater cognitive impairment.

§ Cumulative Illness Rating Scale: higher score = greater organ system burden.

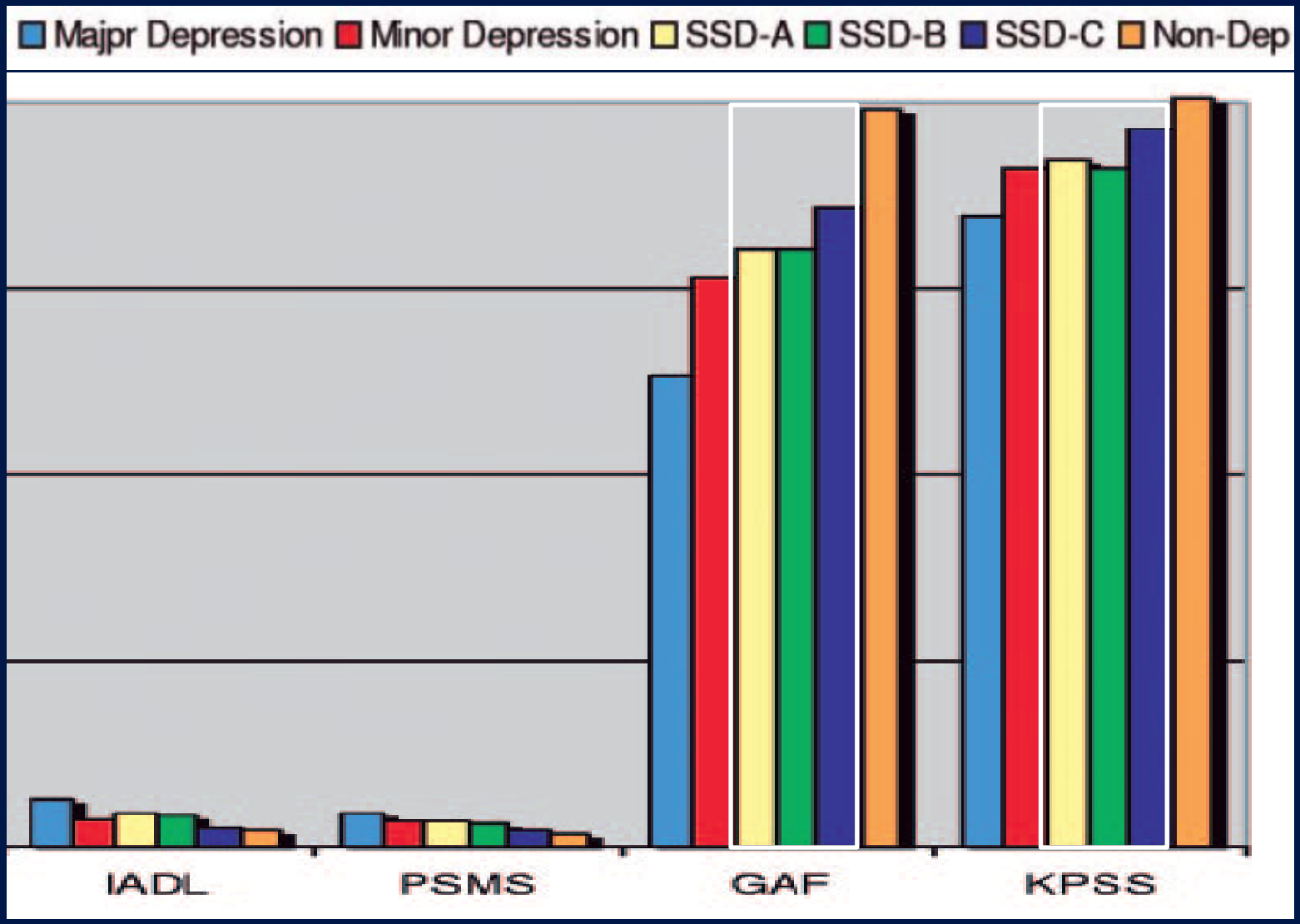
¶ Karnofsky Performance Status Scale: lower score = greater functional impairment judged due to physical factors.

‖ Instrumental Activities of Daily Living: higher score = greater overall functional impairment.

Physical Self-Maintenance Scale: higher score = greater overall functional impairment.

Lyness et al., JAGS 1999

Functional Impairments associated with Subsyndromal Depression in Late-Life



Lyness et al., AJGP 2007

Decline of Physical Function

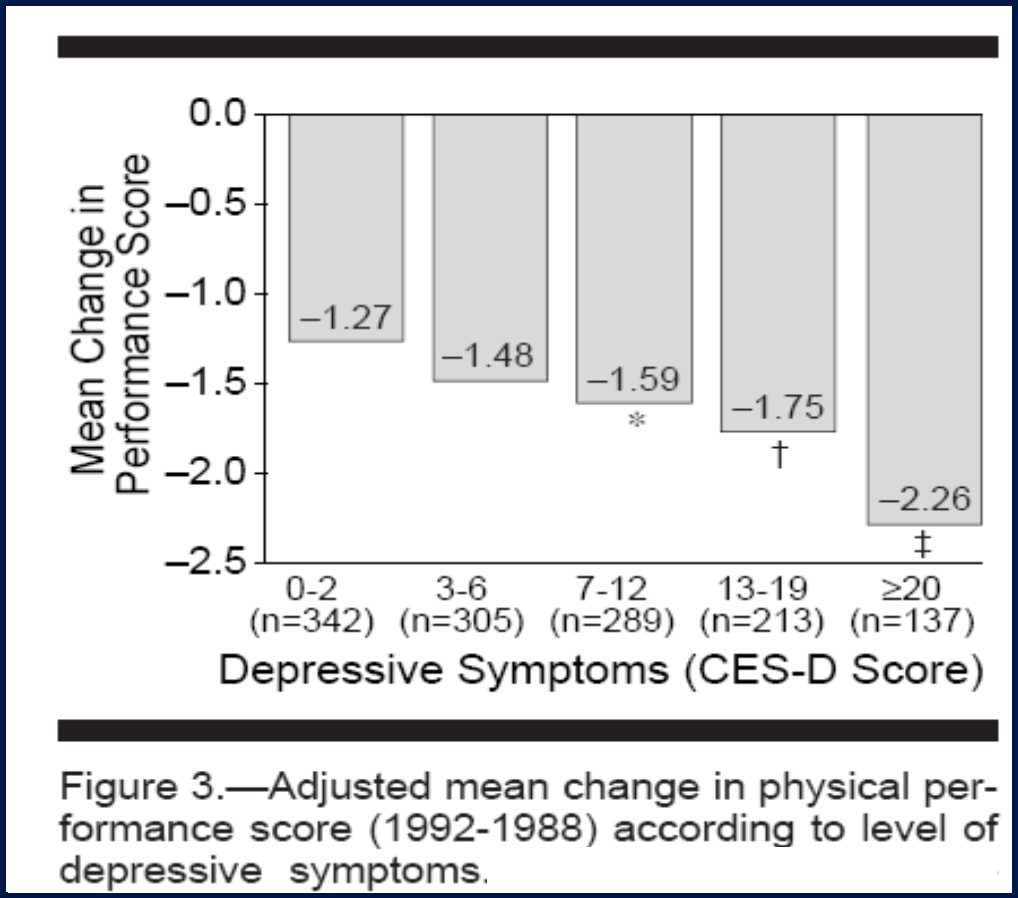


Figure 3.—Adjusted mean change in physical performance score (1992-1988) according to level of depressive symptoms.

JAMA 1998;279:1720-1726

Increased Care Cost associated with Non-Major Depression

TABLE 3. Weekly Hours and Yearly Cost of Informal Care Received by Respondents to a Nationally Representative Survey of Elderly Americans, by Number of Reported Depressive Symptoms in the Last Week (N=6,649)[a]

Respondents Grouped by Number of Depressive Symptoms	Weekly Hours: Adjusted Number of Hours[b]	Weekly Hours: 95% CI	Yearly Cost ($): Adjusted Cost[c]	Yearly Cost ($): 95% CI
None (N=2,531)	2.9	2.8–3.1	1,240	1,200–1,330
1–3 (N=2,954)	4.3	4.1–4.4	1,840	1,750–1,880
4–8 (N=1,164)	6.0	5.7–6.2	2,570	2,440–2,650

Langa et al., Am J Psychiatry 2004

Associated factors of SSD at KLoSHA baseline

Factor	Odds ratios (95% confidence interval)		
	MDD	MnDD	SSD
Women	3.55 (1.53-8.24)*	2.68 (1.19-6.04)*	2.46 (1.34-4.52)**
Socioeconomic status			
Not educated	2.75 (1.30-5.85)*	1.39 (0.60-3.20)	1.48 (0.77-2.83)
Low income (≤$12,000/year)	2.83 (1.02-7.88) *	1.75 (0.68-4.47)	0.69 (0.37-1.30)
Sensory disturbance			
Hearing disturbance (HHIE≥8)	2.29 (1.12-4.68)*	0.88 (0.37-2.12)	1.24 (0.68-2.26)
Prior major depressive episode	3.08 (1.37-6.89)**	3.45 (1.49-8.01)**	1.04 (0.42-2.57)
Cerebral vascular disease			
Stroke or transient ischemic attack	3.45 (1.62-7.35)**	2.95 (1.34-6.52) **	2.12 (1.12-4.19)*
Dementia			
Alzheimer's disease‡	7.00 (2.07-23.62)**	-	2.14 (0.62-7.32)

* P<0.05, ** P<0.01, ***P<0.001, by multinominal logistic regression analysis

Results from KLoSHA

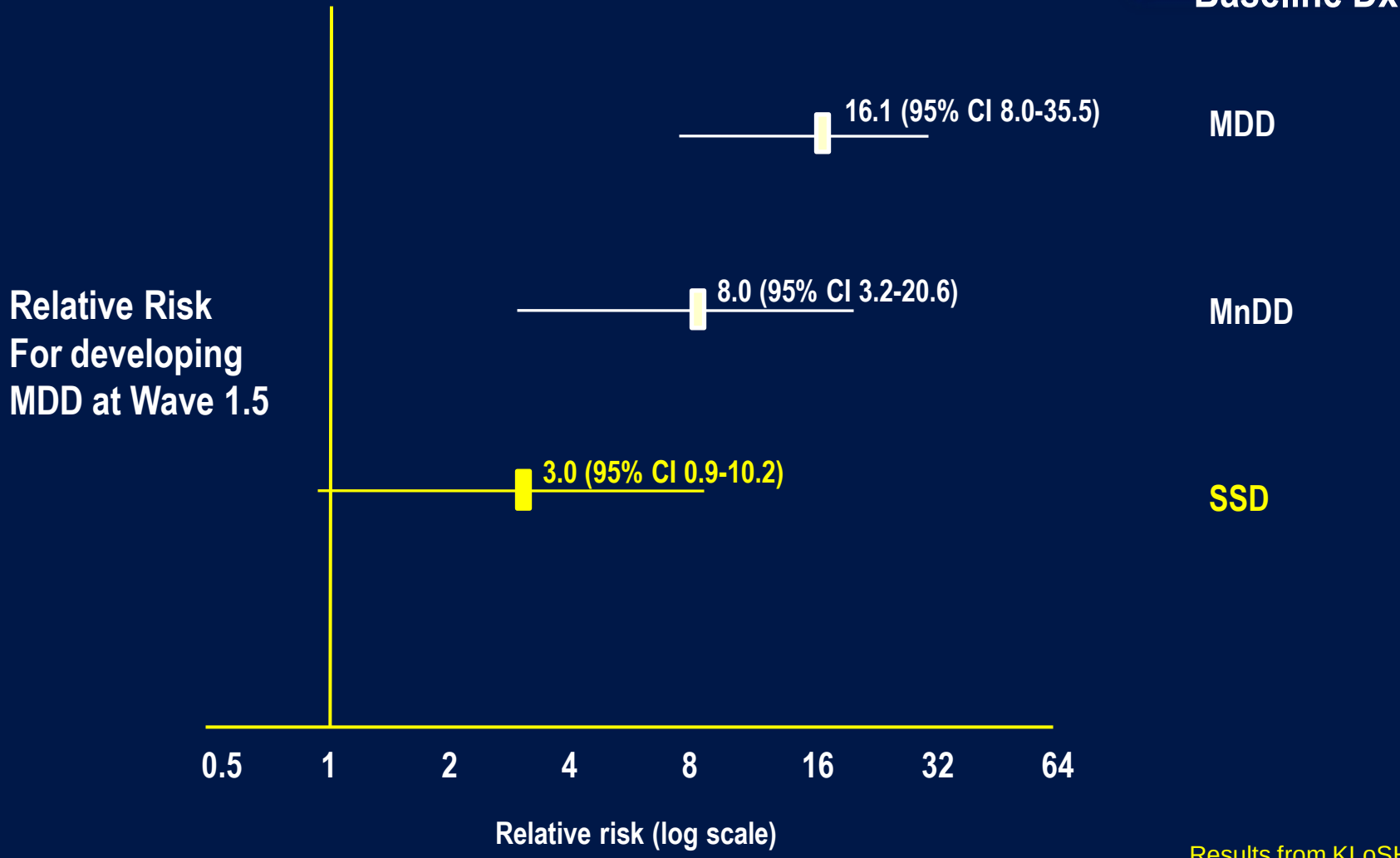
Risk factors for developing SSD at KLoSHA 1.5

Factor	Relative risk (95% confidence interval)	
	MDD/MnDD	SSD
Women	2.03 (0.88-4.66)	2.03 (0.92-4.48)
Socioeconomic status		
Not educated (0 year)	1.54 (0.59-4.03)	0.91 (0.33-2.50)
Low income (≤$12,000/year)	3.13 (1.25-7.81)*	1.65 (0.63-4.31)
Never married/ widowed/ divorced	1.54 (0.57-4.21)	1.94 (0.78-4.87)
Depression		
GDS (≥15)	6.17 (2.58-14.7)**	9.09 (3.84-21.28)**
CES-D (≥17)	7.69 (3.16-18.52)**	6.02 (2.67-13.51)**
HAM-D (≥5)	7.09 (2.80-18.18)**	1.41 (0.62-3.27)
Prior major depressive episode	3.50 (1.12-10.87)*	0.78 (0.17-3.62)
Stroke or transient ischemic attack	1.16 (0.32-4.13)	1.30 (0.42-4.03)
Heart disease	0.94 (0.20-4.37)	2.71 (0.91-8.06)
Hypertension	0.82 (0.36-1.88)	1.24 (0.57-2.73)
DM	0.33 (0.04-2.51)	1.51 (0.52-4.35

* P<0.05, **P<0.001, by multinominal logistic regression analysis

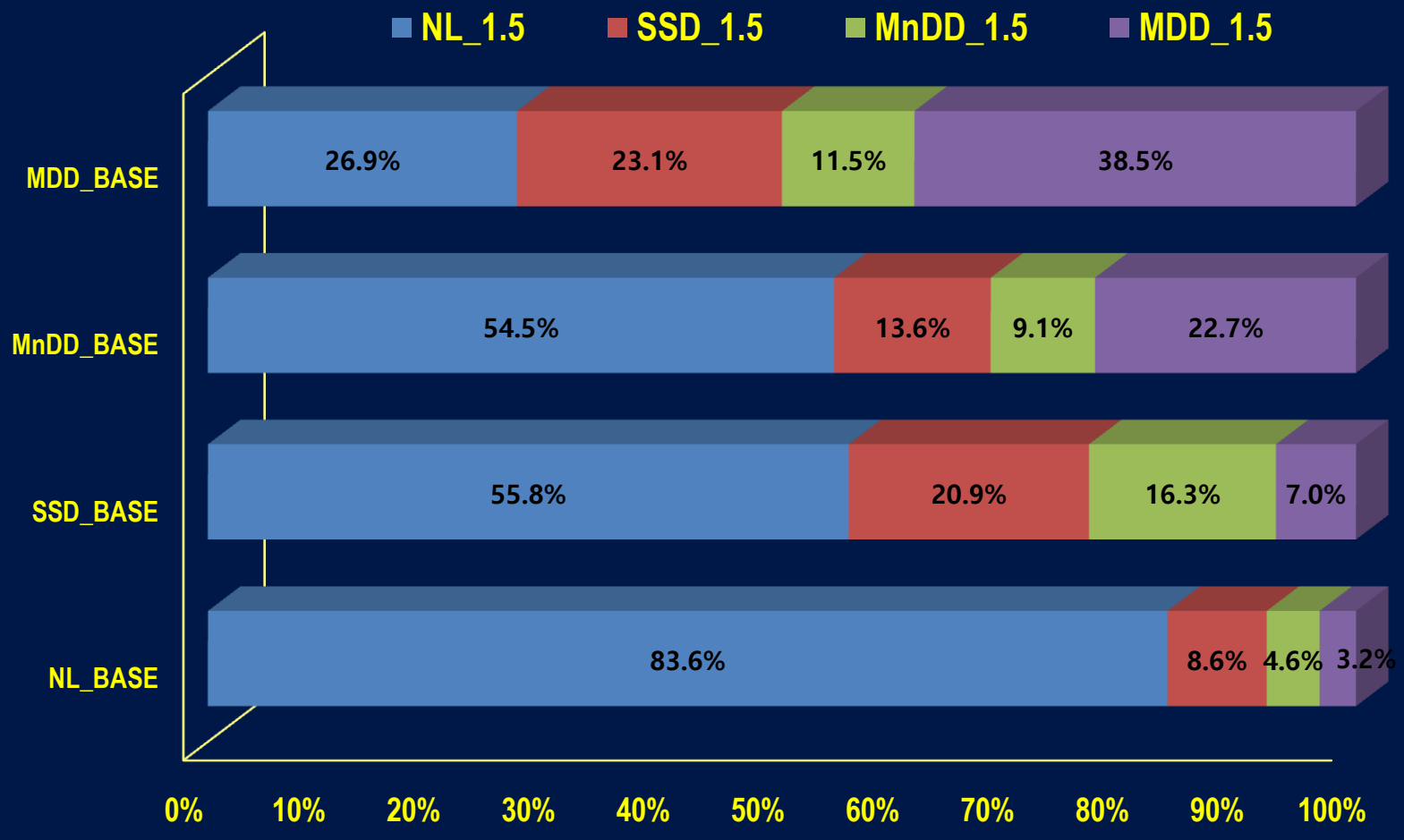
Results from KLoSHA

Relative Risk for developing depressive disorders at wave 1.5



Results from KLoSHA

Change of depression between baseline and wave 1.5



Results from KLoSHA

One year outcome: Depression Diagnosis

Outcomes of Minor and Subsyndromal Depression among Elderly Patients in Primary Care Settings

Table 2. Outcomes at 1 Year by Baseline Depression Diagnosis*

Initial Depression Diagnosis	Depression Diagnosis at 1 Year, *n*†					Total
	Major Depression	Minor or Subsyndromal Depression			Nondepressed	
		Minor Depression	Non–DSM-IV Subsyndromal Depression	Dysthymic Disorder		
Major depression	36	31	30	2	22	121
Minor or subsyndromal depression						
Minor depression	10	19	31	3	23	86
Non–DSM-IV subsyndromal depression	7	17	33	0	44	101
Dysthymic disorder	4	1	3	6	1	15
Nondepressed	1	8	19	2	83	113
Total	58	76	116	13	173	436‡

Lyness et al., Ann Intern Med 2006

Is SSD a part of longitudinal course of MDD?

- A history of MDD in SSD patients
  - No association with SSD
    - Chopra, Zubritsky, Knott*, et al*, 2005
    - Kim et al, 2006, unpublished
    - Lyness, 2007
  - Association with SSD
    - Odds ratio : 2.8 in SSD vs. 274 in MDD (Judd et al., 1997)
- SSD is a risk factor for developing MDD in future
- SSD reflects the characteristics of late onset LLD
  - Start in mild form of depression and can progress to more severe form of depression
  - SSD can be starting point of late onset LLD
  - It is unlikely that SSD is a sort of partial remission of MDD

Conclusions

- Subsyndromal depression
  - Is very prevalent in elderly
  - Is associated with adverse physical and mental health, poor clinical outcomes, social dysfunction and disability and uses of medical and mental health services in the elderly
  - Increased risk for future mood disorders
  - May develop in old age independent of history of MDD and progress to more severe depression in the future
  - Is clinically important in old age, considering its prevalence and longitudinal progression and its impacts

- The further studies are required to prove the internal validity and external validity of operationally defined SSD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Thank you for your attention