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Stability of the subtypes of major depressive disorder in older adults and the influence of mild cognitive impairment on the stability

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THESE

préparée sous la direction du Professeur Armin von Gunten,
et la collaboration du Professeur Martin Preisig.

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par

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Stability of the Subtypes of Major Depressive Disorder in Older Adults and the Influence of Mild Cognitive Impairment on the Stability

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ABSTRACT

Objectives: *To assess 1) the longitudinal stability of the atypical, melancholic, combined atypical-melancholic and the unspecified subtypes of major depressive disorder (MDD) according to the diagnostic and statistical manual of mental disorders (DSM −IV) specifiers in older adults, and 2) the effect of mild cognitive impairment (MCI) on the stability of these subtypes.* ***Design:*** *Prospective cohort study with a 5.1 year-follow-up.* ***Setting:*** *Population-based cohort from Lausanne, Switzerland.* ***Participants:*** *A total of 1,888 participants (mean age: 61.7 years, women: 69.2%) with at least two psychiatric evaluations, one after the age of 65 years.* ***Measurements:*** *Semistructured diagnostic interview to assess lifetime and 12-month DSM-IV Axis-1 disorders at each investigation and neuro-cognitive tests to identify MCI in participants aged 65 years and over. Associations between lifetime MDD status before and 12-month depression status after the follow-up were assessed using multinomial logistic regression. The effect of MCI on these associations was assessed by testing interactions between MDD subtypes and MCI status.* ***Results:*** *1) Associations between depression status before and after the follow-up were observed for atypical (adjusted OR [95% CI] = 7.99 [3.13; 20.44]), combined (5.73 [1.50; 21.90]) and unspecified (2.14 [1.15; 3.98]), but not melancholic MDD (3.36 [0.89; 12.69]). However, there was a certain degree of overlap across the subtypes, particularly between melancholic MDD and the other subtypes. 2) No significant interactions were found between MCI and lifetime MDD subtypes regarding depression status*

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after follow-up. ***Conclusion:*** *The strong stability of the atypical subtype in particular highlights the need for identifying this subtype in clinical and research settings, given its well-documented links to inflammatory and metabolic markers.* (Am J Geriatr Psychiatry 2023; 31:503−513)

Highlights

- **What is the primary question addressed by this study?**
  Are the subtypes of major depressive disorder according to the diagnostic and statistical manual of mental disorders (DSM-IV) specifiers stable in advanced age and what is the influence of mild cognitive impairment on this stability?
- **What is the main finding of this study?**
  Longitudinal stability into advanced age of the atypical and the combined subtypes but not of the melancholic subtype of major depressive disorder according to the DSM-IV specifiers and absence of the effect of mild cognitive impairment on this stability.
- **What is the meaning of the finding?**
  Additional support for the validity of the atypical subtype of major depressive disorder according to the DSM-IV specifier in older age.

OBJECTIVE

With a lifetime prevalence of 15%−18%, major depressive disorder (MDD) is a frequent but also a highly recurrent disorder.[1] The risk of recurrence has been found to reach up to 80%.[2,3] However, MDD is also a heterogeneous disorder in terms of symptom manifestations, course and response to pharmacological treatment[4,5] with presumably a considerable number of underlying, interrelated etiologic pathways.[6] This heterogeneity has hampered research designed to identify the determinants of this disorder. Accordingly, studying subtypes of MDD rather than the disorder as a whole is likely to be a promising approach. Indeed, it has been hypothesized that the symptom-based atypical and melancholic depression subtypes are differently associated with biological mechanisms: the atypical subtype, mainly characterized by increased appetite and hypersomnia, could be more strongly related to the metabolic syndrome and inflammation up-regulation, whereas the melancholic subtype could be related to dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis.[4,7−10]

Aside from testing the specificity of the familial aggregation of depression subtypes, which has been demonstrated for atypical but not for melancholic depression,[11] establishing their longitudinal stability would be a most pertinent demonstration of their diagnostic validity. However, up to this day only a few studies, with a large variance in methodology, have provided such data. These studies either relied on the diagnostic and statistical manual of mental disorders (DSM-IV) specifiers to define the atypical and the melancholic subtypes or used latent class analysis (LCA) to define these two subtypes. In the Zurich cohort study, the stability of the 12-month prevalence of depression subtypes according to the DSM-IV specifiers was established in young adults from the community across 20 years with six assessments from ages 20/21 to 40/41 years.[12] Combining subthreshold and DSM-IV diagnoses of depression due to the small number of people in the diagnostic groupings, the authors found a 8%−12% change from melancholic to atypical depressive syndromes or vice versa across the follow-up period.

Two other cohort studies carried out in the Netherlands were based on clinical samples, used LCA-derived definitions of depression subtypes and had a short follow-up of only 2 years. The first study including a subsample of the NESDA cohort with 12-month MDD at baseline and follow-up identified three

subtypes, a moderate typical, a severe typical and a severe atypical subtype.[13] In this cohort aged around 40 years at baseline, latent transition analysis revealed the highest stability across the follow-up for the atypical subtype (79%). The second study included 111 treated patients with a mean-age of nearly 71 years at baseline.[14] LCA provided an atypical symptom pattern including appetite/weight gain and a melancholic pattern including appetite/weight loss. A latent transition analysis suggested high stability of both subtypes with an estimated transition probability of melancholic to atypical of 0.14, and of atypical to melancholic of 0.07. In the latter study, despite the advanced age of the cohort, the question of the potential influence of mild cognitive impairment (MCI) on the stability of depression subtypes in advanced age was not addressed. Indeed, the occurrence of MCI could impact the manifestation of depression symptoms and thereby affect the longitudinal stability of depression subtypes. According to a study on 322 people with and 322 people without depression, a significantly higher risk of dementia in those with melancholic features across a 20-year follow-up was observed, and hence cognitive deficits might affect the stability of this subtype.[15]

Using data from a prospective population-based cohort that had reached the age of 65 years and older, the goals of the present paper were to assess 1) the longitudinal stability of the atypical, the melancholic, the combined atypical and melancholic and the unspecified subtypes of MDD according to the DSM-IV specifiers across a 5-year follow-up period, and 2) the effect of the MCI status at follow-up on the longitudinal stability of these subtypes. In contrast to the DSM-IV that implies that episodes simultaneously meeting criteria for both atypical and melancholic should be considered as major depressive episodes (MDE) without these specifiers (unspecified), we kept this combined category of people separate and determined its longitudinal stability. We hypothesized that 1) longitudinally and cross-sectionally combined MDD at baseline is associated with cross-sectionally combined, atypical and melancholic MDE at follow-up, 2) atypical MDD at baseline is associated with atypical MDE at follow-up, 3) melancholic MDD at baseline is associated with melancholic MDE at follow-up, 4) unspecified MDD at baseline is associated with unspecified MDE at follow-up and 5) the presence of MCI at follow-up diminishes the associations between the subtype diagnoses at baseline and follow-up.

METHODS

Data Source and Study Sample

The present data stem from CoLaus|PsyCoLaus, a prospective cohort study designed to assess cardiovascular risk factors and mental disorders in the community as well as their associations. The methodological features of the recruitment and baseline assessments of this study were previously described in detail.[16,17] Briefly, CoLaus|PsyColaus includes an initial random sample of 6,734 35−75 year-old participants selected from the general population according to the civil register of the city of Lausanne (Switzerland) between 2003 and 2007. After the baseline investigation, the cohort was followed-up after approximately 5 (follow-up 1, FU1), 9 (follow-up 2, FU2) and 13 years (follow-up 3, FU3). From FU1 on, participants aged 65 years and over were invited to also undergo a series of cognitive tests. A total of 1,893 participants had at least two psychiatric evaluations of which at least one had been completed after the age of 65 years. Among these participants, five needed to be excluded because of incomplete data on MDD, resulting in a sample of 1,888 participants for the analysis testing the stability of MDD subtypes.

Within this sample, 513 had no or incomplete data on cognition resulting in a subsample of 1,375 participants for the analysis on the effect of cognitive deficits on the stability of MDD and its subtypes.

Assessments

Mental disorders at the baseline and follow-up evaluations were assessed using the French version[18] of the semistructured diagnostic interview for genetic studies (DIGS).[19] The DIGS assesses a wide spectrum of DSM-IV Axis-I criteria including for mood, psychotic, substance use and anxiety disorders. The inter-rater and test−retest reliability of both the original English[19] and the French versions,[20] of this instrument were extensively tested for psychotic, mood disorders and substance use disorders. The French version revealed kappa values of 0.93 for inter-rater and 0.62 for test−retest reliability for MDD.[20] For

alcohol and drug use disorders the kappa values for inter-rater reliability were 0.98 and 1.0, respectively, and those for test−retest reliability were 0.72 and 0.93, respectively.[21] The DIGS was completed with the anxiety disorder sections for generalized anxiety disorder and phobias of the French version[22] of the schedule for affective disorders and schizophrenia-lifetime and anxiety disorder version (SADS-LA).[23] The French translation of the SADS-LA was found to have satisfactory test−retest reliability for panic disorder/agoraphobia (Yule's Y = 0.43), GAD (Yule's Y = 0.61) and phobic disorders (Yule's Y = 0.66).[22] Diagnoses were assigned according to the DSM-IV,[24] which also includes specifiers for atypical or melancholic features during MDE. The specifier for atypical features requires mood reactivity and two of the following criteria: weight gain or increase in appetite, hypersomnia, leaden paralysis and interpersonal rejection sensitivity. The melancholic specifier requires a loss of pleasure or lack of reactivity and three of the following criteria: distinct quality of depressed mood, depression worse in the morning, early-morning awakening, psychomotor agitation or retardation, weight loss or guilt. We could not take into account the criterion 'distinct quality of depressed mood' because it was not assessed in the DIGS.

According to these specifiers, each MDE was classified into 1) atypical, 2) melancholic, 3) combined atypical-melancholic (meeting criteria for both atypical and melancholic during an episode) and 4) unspecified (not meeting criteria for atypical or melancholic). Extending the approach suggested by Angst et al.,[12] for the baseline assessment (assessment prior to that including the cognitive evaluation and independent variable in the statistical models) lifetime MDD was subtyped according to the occurrence of subtypes of episodes across lifespan into: 1) atypical MDD with at least one atypical (but no melancholic or combined) episode; 2) melancholic MDD with at least one melancholic (but no atypical or combined) episode; 3) cross-sectionally combined MDD with at least one atypical-melancholic combined episode; 4) longitudinally combined MDD with at least one atypical and one melancholic episode; and 5) unspecified MDD with neither atypical nor melancholic episodes. For the follow-up assessment (assessment including the cognitive evaluation and the dependent variable in the statistical models) we classified the 12-month MDE according to the previously provided definitions for MDE into 1) atypical, 2) melancholic, 3) combined atypical-melancholic and 4) unspecified.

The DIGS also allows assessing a series of clinical features such as the age of onset of MDD, the number of and time spent in MDE, and the global assessment of functioning (GAF) score. Additional information was collected on sociodemographic characteristics. The level of the socioeconomic status (SES) was determined using the Hollingshead scale,[25] which takes into account the participant's professional and educational level. According to the score on this scale, participants can be categorized into 5 social classes with class 3 representing the middle class.

The administered cognitive tests included: Grober and Buschke Double Memory Test (DMT) for episodic memory,[26] DO40 picture-naming test for verbal fluency,[27] Stroop Test for executive processing,[28] and figures drawing from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological test battery for constructional praxis.[29] Furthermore, the clinical dementia rating (CDR)[30] was used to evaluate cognitive functioning taking into account six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Mild cognitive impairment was clinically defined as a score of 0.5 on the CDR.

Interviewers were master-level psychologists trained over a 1 to 2-month period. An experienced senior psychologist reviewed all interviews. A specialized neuropsychologist double-checked all the cognitive assessments.

Statistical Analysis

For participants with more than two psychiatric evaluations, the 12-month diagnosis at the first evaluation with cognitive testing was used as the outcome and the cumulative lifetime diagnosis at the previous evaluation was used as the baseline for the present analyses. Univariate analyses using χ^2 tests for categorical variables and Kruskall-Wallis test/ANOVA for continuous variables were performed to compare the 6 lifetime MDD groups (atypical, melancholic,

combined cross-sectional, combined longitudinal, unspecified, never depressed) at the baseline. In order to assess the association between lifetime MDD subtype status at baseline (independent variable) and the 12-month MDD subtype status at follow-up (dependent variable), two multinomial logistic regression models were used: Model 1 adjusted for sex and age at the first evaluation with cognitive testing, Model 2 also adjusted for SES, length of follow-up, as well as lifetime anxiety disorders (agoraphobia, panic disorder, generalized anxiety disorder, social phobia) and substance use disorders (alcohol, illicit drug) assessed at baseline.

In order to assess the effect of MCI on the prospective associations between lifetime MDD subtypes at baseline and 12-month MDD status at follow-up, we tested the interactions between MCI status at follow-up and lifetime MDD subtypes at baseline in the multinomial logistic regression model with the previously enumerated adjustments of Model 2.

Statistical analyses were computed using the Statistical Analysis System, version 9.4 (SAS Institute, Inc., Cary, NC) and R package brglm2.[31]

Ethics

The institutional Ethics Committee of the University of Lausanne, which afterwards became the Ethics Commission of the Canton of Vaud (www.cer-vd.ch), approved the baseline CoLaus|PsyColaus study (reference 16/03; 134-03,134-05bis, 134-05-2to5 addenda 1to4). The approval was renewed for the first (reference 33/09;239/09), second (reference 26/14; 239/09 addendum 2) and third (PB_2018-00038; 239/09 addenda 3to4) follow-ups. The study was performed in agreement with the Helsinki declaration and its former amendments and in accordance with the applicable Swiss legislation. All participants signed a written informed consent.

RESULTS

Characteristics of Participants

The characteristics of the participants across the 5 lifetime MDD subtype groups are presented in Table 1. A total of 737 participants (39%) met criteria for lifetime MDD. Among them, 13.3% had atypical features, 26.7% melancholic features, 9.1% atypical and melancholic features in the same episode (combined cross-sectional), 4.6% atypical and melancholic features in different episodes (combined longitudinal), and 46.3% had never had episodes with atypical or melancholic features (unspecified MDD). The groups differed with respect to age at the first evaluation, age at the beginning of the follow-up, number of evaluations at the beginning of the follow-up, age at the outcome evaluation (age 65 years and over), sex, as well as all MDD course characteristics and a lifetime history of anxiety disorders. A total of 3.7% of participants were of non-Caucasian origin.

Associations between Lifetime MDD Subtypes at Baseline and 12-month MDD Subtypes at the Consecutive Assessment

Associations between lifetime MDD subtypes at baseline and 12-month MDD subtypes at the consecutive assessment are presented in Table 2 and Figure 1. Among participants meeting criteria for lifetime atypical MDD at baseline, 16.3% reported a depressive episode at follow-up. Among them, almost half experienced a new atypical episode (8.2%) corresponding to an almost 8 times increased risk to report this type of episode at follow-up after adjust adjustment for age at the first evaluation with cognitive testing (Model 1) and according to the fully adjusted model (Model 2). However, although melancholic episodes occurred less frequently (3.1%) in participants with atypical MDD at baseline, there was still a highly significant more than sixfold increase of this type of episode according to both Models 1 and 2.

Within the group of participants with lifetime melancholic MDD at baseline, 15.7% reported a new episode at follow-up. Among them three out of four reported an unspecified episode, which corresponded to a more than five times elevated risk of this type of episode regardless of the adjustments. In contrast, there was no increased risk for any other type of episode including melancholic episodes in these participants.

According to Models 1 and 2, lifetime MDD with atypical and melancholic features in the same episode (combined cross-sectional) at baseline was associated with an elevated risk for both melancholic and

TABLE 1. Characteristics of the Participants (n =1888)

		Lifetime Major Depressive Disorder Subtypes at Baseline						Comparison Across 6 Groups	
	MDD all (n = 737)	Atypical (n = 98)	Melancholic (n = 197)	A-M cross-sectional (n = 67)	A-M Longitudinal (n = 34)	Unspecified (n = 341)	No MDD (n = 1,151)	Test Statistic	p
Sociodemographic characteristics									
Age at first evaluation, mean (s.d.)	61.7 (7.1)	60.5 (6.8)	61.8 (7.0)	61.0 (5.4)	55.3 (3.6)	62.8 (7.4)	64.7 (8.2)	F_5=19.6	<0.001
Age at the beginning of the follow-up, mean (s.d.)	64.5 (5.1)	64.2 (4.6)	64.5 (4.9)	63.4 (3.8)	62.5 (2.1)	65.1 (5.6)	66.6 (6.4)	F_5=12.5	<0.001
Number of evaluations at the beginning of the follow-up, mean (s.d.)	1.5 (0.7)	1.7 (0.8)	1.5 (0.7)	1.5 (0.6)	2.4 (0.7)	1.4 (0.7)	1.4 (0.6)	F_5=20.1	<0.001
Age at the outcome evaluation, mean (s.d.)	69.7 (4.8)	69.3 (4.5)	69.6 (4.8)	68.6 (3.2)	66.8 (1.5)	70.3 (5.3)	71.7 (6.3)	F_5=14.3	<0.001
Female sex, % (n)	69.2 (510)	74.5 (73)	67.5 (133)	77.6 (52)	82.4 (28)	65.7 (224)	50.7 (584)	χ^2_5=70.3	<0.001
SES[a], mean (s.d.)	3.4 (1.2)	3.1 (1.2)	3.4 (1.2)	3.2 (1.1)	3.3 (1.1)	3.5 (1.2)	3.4 (1.2)	F_5=1.7	n.s.
Duration of follow-up, mean (s.d.), years	5.1 (1.8)	5.1 (2.1)	5.1 (1.6)	5.1 (1.9)	4.3 (1.5)	5.2 (1.8)	5.1 (1.7)	F_5=1.9	n.s.
MDD course characteristics									
Age of onset, mean (s.d.)	40.1 (15.9)	41.3 (16.4)	39.2 (16.1)	36.8 (15.3)	32.0 (15.4)	41.7 (15.5)	NA	F_4=4.1	0.003
Number of episodes, median (IQR)	1.0 (1.0;2.0)	2.0 (1.0;3.0)	2.0 (1.0;3.0)	2.0 (1.0;3.0)	3.0 (3.0;5.0)	1.0 (1.0;2.0)	NA	χ^2_4=96.8	<0.001
Time spent in episode, median (IQR), weeks	101.9 (30.0;239.9)	104.3 (42.9;251.4)	100.0 (33.0;217.1)	121.5 (55.7;312.9)	418.5 (190.7;1354;7)	65.0 (25.7;182.1)	NA	χ^2_4=55.0	<0.001
GAF score, mean (s.d.)	45.7 (10.9)	45.4 (11.3)	43.9 (11.5)	40.9 (9.8)	40.9 (8.7)	48.2 (10.3)	NA	F_4=11.3	<0.001
Lifetime psychiatric disorders									
Any anxiety disorder[b], % (n)	21.4 (158)	29.6 (29)	19.8 (39)	34.3 (23)	26.5 (9)	17.0 (58)	10.4 (120)	χ^2_5=63.9	<0.001
Substance abuse or dependence, % (n)	10.9 (80)	11.2 (11)	14.2 (28)	10.5 (7)	5.9 (2)	9.4 (32)	8.4 (97)	χ^2_5=7.6	n.s.
Mild cognitive impairment [c]									
Clinical Dementia Rating ≥0.5, % (n)	43.4 (228)	34.9 (22)	47.3 (69)	40.8 (20)	36.8 (7)	44.2 (110)	50.9 (432)	χ^2_5=10.6	n.s.

Notes: A-M: atypical and melancholic; GAF: global assessment of functioning; IQR: interquartile range; MDD: major depressive disorder; NA: not applicable; n.s.: not significant; s.d.: standard deviation; SES: socioeconomic status.

χ^2/F: chi-square tests (dichotomous variables) or Kruskal-Wallis test (continuous variables)/ANOVA (continuous variables).

[a] A value of 3 represents a middle class SES on the Hollingshead Scale.

[b] Generalized anxiety disorder, social phobia, panic disorder, or agoraphobia.

[c] N = 1,375

TABLE 2. Association Between Lifetime Major Depressive Disorder Subtypes at Baseline and 12-Month Subtypes at the Consecutive Investigation (N =1,888).

	12-Month Major Depressive Episode Subtypes at Follow-up												
	Atypical			Melancholic			A-M cross-sectional			Unspecified			No MDD
	Model 1		Model 2	Model 1		Model 2	Model 1		Model 2	Model 1		Model 2	
Exposure	% (n)	OR[a] (95CI)	OR[b] (95CI)	% (n)	OR[a] (95CI)	OR[b] (95CI)	% (n)	OR[a] (95CI)	OR[b] (95CI)	% (n)	OR[a] (95CI)	OR[b] (95CI)	% (n)
Lifetime MDD subtypes at baseline													
Atypical	8.2 (8)	**7.97***** **(3.09;20.51)**	**7.99***** **(3.13;20.44)**	3.1(3)	**6.83**** **(1.73;26.88)**	**6.94**** **(1.79;26.92)**	1.0 (1)	2.19 (0.37;13.11)	1.87 (0.33;10.54)	4.1 (4)	1.92 (0.68;5.45)	1.76 (0.62;5.03)	83.7 (82)
Melancholic	1.0 (2)	1.21 (0.30;4.87)	1.30 (0.33;5.06)	1.5 (3)	3.69 (0.96;14.25)	3.36 (0.89;12.69)	1.5 (3)	2.62 (0.71;9.65)	2.30 (0.65;8.15)	11.7 (23)	**5.34***** **(2.95;9.66)**	**5.31***** **(2.93;9.65)**	84.3 (166)
A-M cross-sectional	1.5 (1)	1.98 (0.34;11.51)	1.95 (0.35;11.04)	6.0 (4)	**13.13***** **(3.54;48.73)**	**13.38***** **(3.54;50.50)**	4.5 (3)	**7.07**** **(1.84;27.21)**	**5.73*** **(1.50;21.90)**	7.5 (5)	**3.60*** **(1.34;9.71)**	**3.39*** **(1.25;9.20)**	80.6 (54)
A-M longitudinal	8.8 (3)	**8.67**** **(2.26;33.24)**	**8.47**** **(2.23;32.11)**	5.9 (2)	**16.13***** **(3.13;83.16)**	**14.95**** **(2.86;78.16)**	0.0 (0)	1.80 (0.09;36.22)	1.87 (0.10;34.87)	14.7 (5)	**8.26***** **(2.83;24.09)**	**9.32***** **(3.17;27.39)**	70.6 (24)
Unspecified	2.1 (7)	2.11 (0.82;5.42)	2.24 (0.89;5.65)	2.9 (10)	**6.04***** **(2.15;16.99)**	**5.57***** **(2.02;15.38)**	0.9 (3)	1.55 (0.43;5.62)	1.49 (0.43;5.17)	5.0 (17)	**2.14*** **(1.15;3.99)**	**2.14*** **(1.15;3.98)**	89.2 (304)
No MDD	0.9 (10)	1 (ref)	1 (ref)	0.4 (5)	1 (ref)	1 (ref)	0.5 (6)	1 (ref)	1 (ref)	2.4 (27)	1 (ref)	1 (ref)	95.8 (1103)

Significant values are bolded.

Notes: A-M: atypical and melancholic; MDD: major depressive disorder; OR: odd ratio; 95CI: 95% confidence interval.

[a] Model 1 adjusted for age at the first evaluation with cognitive testing and sex.

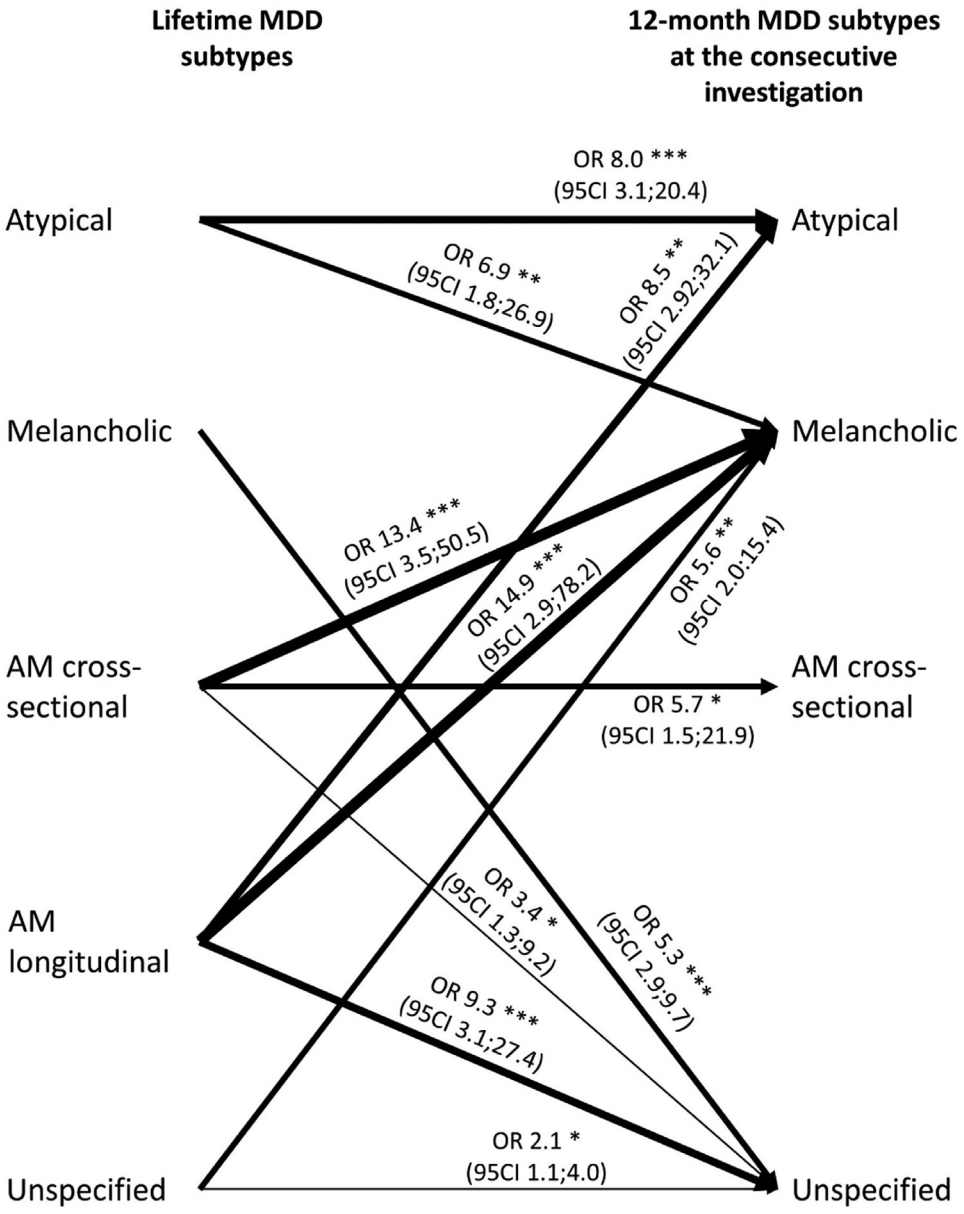
[b] Model 2 adjusted for age at the first evaluation with cognitive testing, sex, socioeconomic status, time between previous interview and first evaluation with cognitive testing, lifetime history of other psychiatric disorders (anxiety disorders and substance abuse or dependence) at baseline.

* $p < 0.05$,

** $p < 0.01$,

*** $p < 0.001$

FIGURE 1. Association between lifetime major depressive disorder subtypes at baseline and 12-month subtypes at the consecutive investigation (n =1,888). OR: odd ratio; 95CI: 95% confidence interval; MDD: major depressive disorder; AM: atypical and melancholic. Model adjusted for age at the first evaluation with cognitive testing, sex, socioeconomic status, time between previous interview and first evaluation with cognitive testing, and lifetime history of other psychiatric disorders (anxiety disorders and substance abuse or dependence) at baseline.* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.



unspecified episodes but also for the recurrence of the same type of episode, whereas the longitudinally combined subtype at baseline entailed elevated risks for atypical, melancholic and unspecified episodes but not for episodes simultaneously meeting atypical and melancholic criteria.

Finally, according to the two adjusted models unspecified MDD at baseline was associated with a

higher likelihood of the occurrence of unspecified but also melancholic episodes.

Interactions between Lifetime MDD Subtypes at Baseline and MCI Status Regarding 12-month MDD Status at the End of the Follow-up

Models testing the effect of MCI status at the end of the follow-up on diagnostic stability did not reveal any significant interactions between lifetime MDD subtypes at baseline and MCI status regarding 12-month MDD status at the end of the follow-up ($p = 0.175, 0.805, 0.919, 0.198, 0.632$ for atypical, melancholic, combined cross-sectional, combined longitudinal and unspecified MDD subtypes, respectively).

CONCLUSIONS

Based on a large population-based prospective cohort and the DSM-IV specifiers, this is the first study testing the longitudinal stability of MDD subtypes in advanced age with assessment of the potential influence of MCI on this stability. The most salient findings were: 1) the confirmation of remarkable longitudinal stability particularly of the atypical subtype and the combined subtype with both atypical and melancholic features during the same episode, and 2) the absence of any effect of the MCI status on this stability. Our data are best comparable with those of the Zurich cohort study given similar diagnostic approaches to subtype MDD and the assessments of cohorts recruited from the community. Our observations of only 4.6% of people with MDD who had a lifetime history of both atypical and melancholic episodes (longitudinal combined subtype) at baseline and the moderate proportion of people who changed between the melancholic and the atypical subtypes during the 5-year follow-up, indicating modest longitudinal overlap between these two subtypes, are essentially consistent with previous findings in the young adults of the Zurich cohort study.[12] They are also in line with those of the two studies conducted in the Netherlands[13,14] despite the use of LCA-derived definitions of subtypes in these studies, which only very loosely match with the DSM-IV criteria for atypical and melancholic episodes.

However, our small proportion of participants with the longitudinally combined MDD subtype at baseline and a relatively short prospective period of approximately three years is likely to underestimate the number of participants with a history of the two types of episodes due to the risk of incomplete recall of episodes. Indeed, this proportion was smaller than that of 17.9% in the Zurich cohort study,[12] in which participants were evaluated six times across 20 years. The very strong likelihood of the recurrence of atypical episodes, together with the observation that only this subtype, and not the other subtypes at baseline, is associated with an increased risk for atypical episodes at follow-up, provided the strongest support for the stability of this subtype in our study. In contrast, we also observed a relatively large proportion of participants with this subtype at baseline who changed from atypical to melancholic, suggesting some degree of overlap between the atypical and melancholic subtypes. Our proportion of 19% was larger than those in the Zurich study (8%) despite a much shorter follow-up and larger than in the Dutch cohort of depressive patients in old age (7%).[14]

In contrast to the atypical subtype, lifetime melancholic MDD was not associated with the reporting of a melancholic episode at follow-up. People with the melancholic subtype at baseline most frequently reported unspecified episodes at follow-up. Conversely, unspecified MDD at baseline also predicted melancholic episodes at follow-up, indicating a strong reciprocal longitudinal overlap between these two MDD subtypes. In contrast, changes from melancholic to atypical were rare among those who also reported a 12-month depressive episode at follow-up (1% of 16.3% = 6.4%) and occurred less frequently than in the Zurich study (12%)[12] and in the Dutch cohort of depressive patients in old age (14%).[14] These findings shed doubt on the longitudinal stability of the melancholic subtype according to the DSM-IV specifier. Although using LCA-derived subtyping, Lamers et al.[13] also reported the highest longitudinal stability for the atypical subtype. Moreover, a family study demonstrated the familial aggregation of the atypical but not the melancholic subtype according to the DSM-IV criteria.[11] The significant associations between the cross-sectionally combined and the unspecified subtypes at baseline and the occurrence of the respective type of episodes also provide some evidence for the

longitudinal stability of these subtypes, which has not been studied before.

In addition to previous studies, we demonstrated that the occurrence of MCI has no influence on the stability of the subtypes. It is likely that the low degree of impairment associated with MCI is not sufficient to significantly affect the symptomatic expression of depressive episodes. Of course, it cannot be excluded that more severe forms of cognitive impairment would have affected the stability of depression subtypes. In our study, the development of MCI was not associated with MDD or any of its subtype at baseline. This contrasts with several previous studies,[15,32] which, however, relied on samples including older people.

The results of this study need to be viewed in the light of several limitations. First, our most important limitation is the advanced age of the first investigation of participants, which entails the risk that the symptoms of remote episodes may not be accurately recalled or episodes may have been entirely forgotten. Second, our diagnostic interview used at the follow-up evaluations elicited the symptoms of only one depressive episode. Therefore, we may have missed the correct assignment of atypical or melancholic episodes in participants reporting more than one episode (18%) during a follow-up interval. Third, the data of the present study are based on an urban sample in Switzerland. However, although the particular features of the sample are likely to affect the prevalence estimates of diseases, they are less likely to significantly affect the estimated stability of the MDD subtypes. Fourth, as our sample included mainly Caucasian participants, generalizability to other racial and ethnic groups cannot be made.

To sum it up, despite some overlap with melancholic MDD, the results of the longitudinal stability of the atypical but not the melancholic subtype of depression in the present study is in line with findings from a recent family aggregation study providing additional support to the validity of the atypical subtype but less of the melancholic subtype according to the DSM-IV specifiers.[11] This longitudinal stability of the atypical subtype persists into old age and is not influenced by MCI. Our study also provides some new evidence for the longitudinal stability of the unspecified and the cross-sectionally combined atypical-melancholic subtypes, although to a lesser extent. The demonstrated longitudinal stability of atypical MDD together with the consistent findings of strong prospective associations between this subtype and inflammatory and metabolic markers,[13,33,34] which are restricted to this depression subtype, highlight the need for identifying this subtype in clinical settings and for a thorough metabolic monitoring in patients affected with this subtype in particular. In future research, the subtyping of depression may also enhance the identification of genetic and environmental factors involved in the development of depression and contribute to a better understanding of the comorbidity of depression with a multitude of mental and somatic disorders.

AUTHOR CONTRIBUTIONS

Substantial contributions to the conception or design of the work by BMP, MP, and AvG. Analysis or interpretation of data for the work by MP, BPM, AvG, MPS, SR, and CV. Initial draft of the work by BPM. Revising the work critically for important intellectual content by all authors. Final approval of the version to be published by all authors. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved by BMP, MP, and AvG.

DATA STATEMENT

The data has been previously presented by poster at the Annual congress of the Swiss Psychiatry and Psychotherapy Society. Bern. September 8, 2022.

DISCLOSURES

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