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This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Published in final edited form as:

Title: Tracing the associations between sex, the atypical and the combined atypical-melancholic depression subtypes: A path analysis.

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Journal: Journal of affective disorders

Year: 2016 Jan 15

Issue: 190

Pages: 807-818

DOI: [10.1016/j.jad.2015.10.067](https://doi.org/10.1016/j.jad.2015.10.067)

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Tracing the associations between sex and the atypical or combined atypical-melancholic depression subtypes: a path analysis

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Manuscript submitted to
Journal of Affective Disorders
(Original paper)

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Abstract

Background:

Numerous studies have examined determinants leading to preponderance of women in major depressive disorder (MDD), which is particularly accentuated for the atypical depression subtype. It is thus of interest to explore the specific indirect effects influencing the association between sex and established depression subtypes.

Methods:

The data of 1624 subjects with a lifetime diagnosis of MDD derived from the population-based PsyCoLaus data were used. An atypical ($n = 256$), a melancholic ($n = 422$), a combined atypical and melancholic features subtype ($n = 198$), and an unspecified MDD group ($n = 748$) were constructed according to the DSM-IV specifiers. Path models with direct and indirect effects were applied to the data.

Results:

Partial mediation of the female-related atypical and combined atypical-melancholic depression subtypes was found. Early anxiety disorders and high emotion-orientated coping acted as mediating variables between sex and the atypical depression subtype. In contrast, high Body Mass Index (BMI) served as a suppression variable, also concerning the association between sex and the combined atypical-melancholic subtype. The latter association was additionally mediated by an early age of MDD onset.

Limitations:

The use of cross-sectional data does not allow causal conclusions.

Conclusions:

This is the first study that provides evidence for a differentiation of the general mechanisms explaining sex differences of overall MDD by depression subtypes. Determinants affecting the pathways begin

early in life. Since some of them are primarily of behavioral nature, the present findings could be a valuable target in mental health care.

Keywords: *Depression, atypical and melancholic subtypes, sex, epidemiology.*

1. Introduction

The impetus to differentiate the psychopathological phenotype of Major Depressive Disorder (MDD) is provided by accumulating empirical evidence demonstrating that this disorder subsumes different symptom clusters/subtypes. Separate lines of studies applying data-driven methodological techniques, such as latent class analysis (Alexandrino-Silva et al., 2013; Kendler et al., 1996; Lamers et al., 2012a; Lamers et al., 2010; Rodgers et al., 2014a; Rodgers et al., 2014b; Sullivan et al., 1998; Sullivan et al., 2002), factor analysis (Li et al., 2014; Serretti et al., 1998), principal components analysis (Basoglu, 1984; Haslam and Beck, 1993) and cluster analysis (Andreasen and Grove, 1982; Fountoulakis et al., 1999; Maes et al., 1990; Schotte et al., 1997) have confirmed the existence of atypical and/or melancholic (also referred to as typical or endogenous) symptom subtypes. Both depression symptom subtypes are included in the current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA, 2013) as MDD specifiers ‘with atypical features’ and ‘with melancholic features’, respectively. The atypical depression subtype was particularly characterized by the presence of either reverse vegetative symptoms of hypersomnia or hyperphagia in a nationally representative sample (Blanco et al., 2012). Beyond their delimitable symptom profiles, and certain psychosocial characteristics, recent studies strongly supported the differentiation of atypical and melancholic depression subtypes with respect to their pathophysiological markers and mechanisms, e.g., obesity (Antonijevic, 2006; Baumeister and Parker, 2012; Gold and Chrousos, 2002; Lamers et al., 2013; Lasserre et al., 2014). Although a consistent body of literature has documented the differentiation of atypical and melancholic depression, the exact etiologic mechanisms of these subtypes are far from being understood. From a longitudinal perspective, the atypical and melancholic/typical subtypes have been shown to be stable, particularly with regard to the atypical group (Lamers et al., 2012b; Rodgers et al., 2014a). However, these two subtypes exhibit a considerable overlap in nearly half of all cases (Angst et al., 2007), and moreover, include a group of subjects fluctuating between atypical and melancholic/typical episodes (Levitan et al., 1997; Rodgers et al., 2014a). The fluctuating group was shown to suffer from affective dysregulation, impulsivity and severe psychopathology (Levitan et al., 1997) and the changing profiles of melancholic and atypical depression profiles were hypothesized to result from a “hypothalamic switch” in the regulation of the hypothalamic-pituitary-adrenal (HPA)

system (O'Keane et al., 2012). However, this hypothesis still needs further validation. In any case, Angst and colleagues (2007) suggested that future research should also consider a combined subgroup comprised of subjects with both atypical and melancholic features.

A particularly interesting feature of these depression subtypes is the marked preponderance of women in atypical depression (Angst et al., 2002; Benazzi, 1999; Halbreich and Kahn, 2007; Moskvina et al., 2008; Posternak and Zimmerman, 2001). So far, few studies have investigated specific mechanisms in relation to the female-related atypical depression subtype. On the other hand, a considerable number of studies have focused on the general mechanisms explaining sex differences of overall MDD (Kuehner, 2003; Piccinelli and Wilkinson, 2000), as illustrated in the following section.

The association between sex and early age of onset of MDD has been reported for women (Kornstein et al., 2000; Marcus et al., 2005; Moskvina et al., 2008; Schuch et al., 2014). Accounting for comorbid conditions, Breslau et al. (1998; Breslau et al., 1995) attributed a considerable portion of the sex differences in MDD to prior anxiety disorders, which are more common in women. In cases where men had been previously affected by anxiety disorders, they were however as vulnerable as women to become depressed. In terms of personality factors, neuroticism was broadly replicated as a robust risk factor for MDD (Boyce et al., 1991; Hirschfeld et al., 1989; Kendler et al., 1993; Sjöholm et al., 2009), particularly among women (Kendler and Gardner, 2014). Moreover, the latter study distinguished low parental warmth, divorce, low social support, and low marital satisfaction as female-related risk factors in the etiologic pathway to MDD, whereas variables such as childhood sexual abuse, prior history of MDD, certain stressful life events (related to financial, work and legal problems) and drug abuse were determined to be male-related risk factors (Kendler and Gardner, 2014). Further evidence with regard to female-associated risk factors for overall MDD stem from studies focusing on coping styles. Emotion-oriented and ruminative coping style were more frequently reported by depressed women than men (Hildebrandt et al., 2003; Nolen-Hoeksema, 2012), and emotion-oriented coping was associated with high depression scores in both sexes (Endler and Parker, 1990; Ravindran et al., 1995). From the large number of proposed coping styles, Parker and Endler (1992) emphasized that many of them could be

clustered around the basic dimensions of problem-orientated coping, emotion-orientated coping and avoidance strategy. While the problem-orientated coping style is directed at reducing or removing a stressor and tends to be used in subjectively controllable situations, emotion-orientated coping is aimed at reducing and managing the emotional distress and tends to be used in uncontrollable appraised situations (Carver et al., 1989; Dunn and Conley, 2015; Folkman and Lazarus, 1980, 1988). A recently published review even found evidence for a genetic variation explaining coping phenotypes, however, these findings are based on sparse data and replication is required (Dunn and Conley, 2015).

With regard to specific mechanisms between sex and atypical depression, Angst et al. (2002) emphasized that the consistently found reports of an earlier age of onset may be an indicator of severity, and that women may have an earlier age at onset of atypical depression. Halbreich and Kahn (2007) revealed the high prevalence of atypical depression during the perimenopause period, suggesting involvement of hormone instability in its pathobiology. Apart from these findings, there is not much knowledge about the reasons for the preponderance of women in atypical depression.

In summary, the perspectives of the risk factors considered can be distinguished as follows: general risk factors focusing on sex-differences of overall MDD (partly also applying to depressed men) on the one hand, versus specific risk factors focusing on sex-differences related to depressive subtypes and sex-specificity, respectively, on the other. Taking into account the explanation of the female-related risk for MDD resulting from the phenotype of atypical depression, we are actually faced with nested risk factors. Based on the growing consensus that atypical depression and melancholic depression are well distinguishable, particularly with regard to weight-/appetite associated features (Benazzi, 2002), there is a need to better understand the links between sex, general and specific risk factors and these MDD subtypes.

In the present study we examined the pathways between sex and the MDD subgroups atypical depression, melancholic depression, a combined subgroup (including subjects with both melancholic and atypical features) and an unspecified MDD group by applying path analysis to a community sample

of Swiss adults. We aimed to clarify the potential mediating or suppressing effects of general and sex-related risk factors, based on the literature (such as age of onset of MDD, comorbid anxiety disorders, substance use, obesity, personality traits, coping styles, childhood adversities, and parental bonding) as regards their influence on the relation between sex and these depression subtypes.

2. Material and methods

2.1 Sample

The data of the current paper stem from the baseline data of the PsyCoLaus study (Preisig et al., 2009), which is the psychiatric branch of the CoLaus study (Firmann et al., 2008). Both PsyCoLaus and CoLaus are prospectively designed cohort studies. A major goal of PsyCoLaus was that to assess data on the prevalence of threshold and subthreshold psychiatric syndromes in the general population (Preisig et al., 2009). In 2003, the participants of CoLaus ($n=6'736$) aged between 35 and 75 years were randomly recruited from the population registry in the city of Lausanne (Switzerland) (Firmann et al., 2008). Clinical data and blood samples were collected and participants were interviewed with a comprehensive semi-structured questionnaire. Sixty-seven percent of the subjects in the age range between 35 and 66 years participating in CoLaus ($n=5'535$) also took part in PsyCoLaus, resulting in a total of 3'720 individuals. For the current study, subjects with a lifetime diagnosis of MDD were selected, resulting in a sample of $n=1624$. All diagnostic interviews were conducted by psychologists or psychiatrists intensively trained over a two-month period and each interview protocol was reviewed by a senior psychologist (Preisig et al., 2009).

2.2 Measurements

2.2.1 Assessment of sociodemographic and clinical measures

2.2.1.1 Face-to-face interview

Sociodemographic characteristics were provided through a standardized interview, and socioeconomic status (SES) was assessed using the Hollingshead scale (Hollingshead, 1975). Information on mental disorders was collected using the semi-structured Diagnostic Interview for Genetic Studies ((DIGS) Nurnberger et al., 1994; Preisig et al., 1999). The DIGS allows for the computation of a broad spectrum of DSM IV (2000) Axis I algorithms, supplemented by sections on anxiety disorders from the Schedule for Affective Disorders and Schizophrenia – Lifetime Version (Endicott and Spitzer, 1978). The depression section of the DIGS provides comprehensive information about the depressive phenomenology during the current/recent/last/ and the most severe depressive episodes. Furthermore, the DIGS records precise information on the course and chronology of comorbid conditions (Preisig et al., 2009). The age of onset of the mental diagnoses was assessed by asking the following DIGS question: “When did it begin?”, based on a metric scale. Abuse of and dependence on alcohol, marijuana, hallucinogens, stimulants, cocaine, sedatives, solvents, and narcotics was grouped in the category substance use as soon as a subject fulfilled the abuse/dependence criteria of one of the corresponding substances. Due to their wide differences in ages of onset, anxiety disorders were grouped into two categories of disorders with comparable ages of onset: early anxiety disorders beginning during childhood or adolescence (< age 16) comprising simple phobia, social phobia, separation anxiety disorder, and overanxious disorder versus late anxiety disorders beginning in adulthood comprising panic disorder, generalized anxiety disorder, and agoraphobia. Subjective judgment of general childhood was rated on a four-point Likert scale ranging from 1 = “happy” to 4 = “very unhappy” in a DIGS section focusing on childhood.

The French translation of the DIGS (Leboyer et al., 1995) showed excellent inter-rater reliability (kappa and Yule’s Y coefficients) for major mood and psychotic disorders (Preisig et al., 1999), substance use disorders and antisocial personality disorders (Berney et al., 2002), and satisfactory inter-rater and test-retest reliability for the anxiety chapters (Leboyer et al., 1991; Rougemont-Buecking et al., 2008). One of several revisions in the French version was the addition of specific criteria to distinguish the MDD *specifier* atypical depression (including leaden paralysis, long-standing patterns of interpersonal rejection sensitivity, mood reactivity) (Preisig et al., 2009).

For the current study, the criteria of the *specifiers* according to the DSM-IV (APA, 2000) were used to diagnose atypical and melancholic depressive episodes. The DSM-IV specifier for atypical depression requires mood reactivity (the capacity to be cheered up when confronted with positive events) and at least two of the following four symptoms: i) increased appetite or significant weight gain, ii) hypersomnia, iii) leaden paralysis (i.e., heavy, leaden feelings in arms or legs), and iv) a long-standing pattern of interpersonal rejection sensitivity. As suggested by Angst and colleagues (2006), atypical depression was diagnosed in a non-hierarchical way meeting at least three out of the five DSM-IV atypical specifier criteria. Only the appetite part of the DSM-IV criterion of increased appetite or weight gain was applied to prevent redundancy due to the fact that BMI (including information about weight gain) was used as a potential mediator/suppressor (M/S) variable in the current study. The DSM-IV specifier for melancholic depression requires either loss of energy or lack of mood reactivity and three out of the following five symptoms: i) depression regularly worse in the morning, ii) early morning awakening, iii) psychomotor retardation or agitation, iv) decreased appetite (without taking into account weight loss as a criterion ****also correct for the current study??****) and v) excessive guilt. The sixth DSM-IV criterion ‘distinct quality of depressed mood’ was not considered because it was not assessed in the DIGS. Four MDD subtypes were derived on the basis of the history of atypical and melancholic episodes in subjects fulfilling the criteria for a lifetime diagnosis of MDD: 1) MDD with atypical features only (at least one episode met criteria for atypical features, but no episode met criteria for melancholic features), 2) MDD with melancholic features only (at least one episode met criteria for melancholic features, but no episode met criteria for atypical features), 3) MDD with combined melancholic and atypical features (at least one episode met criteria for atypical features and one episode met criteria for melancholic features), and 4) unspecified MDD (no episode met criteria for atypical or melancholic features).

2.2.1.2 Self-rating questionnaires

The French translation of the EURONET: Problem Resolution Strategy was used to assess subjective coping strategies (Bodmer and Grob, 1996; Grob et al., 1993). This self-rating questionnaire consists of

17 items on possible reactions to problematic situations rated on a four-level Likert scale, ranging from “very usual for me” to “very unusual for me”. According to our own validation study (Perrin et al., 2014), the items of the EURONET can be divided into the three broad domains of *emotional problem resolution strategy* (9 items), *active problem resolution strategy* (4 items), and *help seeking behaviors* (4 items). The standardized Cronbach’s alpha coefficients were 0.65 (emotion-focused coping), 0.69 (Help-seeking), and 0.44 (problem-focused coping), respectively (Perrin et al., 2014).

Information concerning personality traits was taken from the Eysenck Personality Questionnaire (EPQ), conceptualizing personality as the three biologically-based independent temperament dimensions Extraversion–Introversion, Neuroticism–Stability, and Psychoticism–Socialization (Eysenck and Eysenck, 1975). The French version of the EPQ was validated by its originators (Eysenck et al., 1980).

In order to measure parental bonding styles, the French version (Mohr et al., 1999) of the Parental Bonding Instrument (PBI) (Mohr et al., 1999; Parker et al., 1979) was applied. The PBI is a self-report instrument with 25 items, assessing the relationship between the subjects up to the age of 16 years and their parents. Similar to other studies, the French version of the PBI showed a three-factor rather than the original two-factor structure to be satisfactory (Mohr et al., 1999). The standardized Cronbach’s alpha coefficients for the facets of the three factors were 0.86 (care), 0.84 (denial of autonomy), and 0.72 (encouragement of freedom), which are assessed in both maternal and paternal forms.

2.2.2 Assessments of physical features

The body mass index (BMI) providing information on adiposity was calculated as weight in kilograms divided by height in meters squared. Subjects were standing and dressed in light indoor clothes but not wearing shoes while measured and weighted. These physical measures were taken after an 8-hour fast and after refraining from exhausting physical activity for the previous 12 hours. For more details with regard to the physical assessment, see Lasserre et al. (2014).

The study was approved by the Institutional Ethics Committee of the University of Lausanne. Based on the declaration of Helsinki, all subjects signed written informed consent after being informed about the goal and funding of the study (Preisig et al., 2009).

2.3 Statistical analysis

Descriptive statistics were provided by absolute and relative frequencies for categorical variables and measures of central tendencies and variability for metric variables, respectively. Chi-square tests were applied to the categorical variables to test for significant frequency differences. Due to the non-normally distributed metric data, nonparametric Kruskal-Wallis rank-sum tests were used. Bivariate associations between depressive subtypes, sex, and potential M/S variables were computed, using multinomial logistic regressions (MLR; odds ratios (ORs) with 95% confidence intervals (CIs)) and non-parametric Mann-Whitney U tests.

Path models were specified treating the variable sex as the independent variable (IV) and the depressive subtypes (four categories: atypical MDD, melancholic MDD, combined atypical-melancholic MDD, and unspecified MDD acting as reference group) as dependent variable (DV). In the context of the mediation analysis, the relationship between an IV and a DV is decomposed into two causal paths, whereby one of these paths links the IV directly to the DV (direct effect) and the other links the IV to the DV through an M/S (indirect effect). The indirect effect implies that an IV causes an M/S and the M/S causes the DV (Holland, 1988; MacKinnon et al., 2000; Sobel, 1990). According to the four criteria of Baron and Kenny (1986) (significant three simple regressions: 1) IV on DV; 2) IV on M/S; 3) M/S on DV; and 4) a multiple regression of IV and M/S on DV, in which M/S remains significant and IV is either no longer significant (full mediation), or still significant but reduced in its strength (partial mediation)) and the definition of MacKinnon, Krull and Lockwood (2000), all variables were examined in terms of potential M or S. Statistical significance of indirect effects were based on Sobel's method (1982) and CI (effect considered significant if the 95% CI did not contain the value 1.0; MacKinnon et al., 2004) in the current analysis. Stone and Sobel (1990) have shown that the standard error is accurate

for samples including a minimum of 100-200 subjects in models with more than one mediator. Similar findings were also found elsewhere (MacKinnon et al., 2007; MacKinnon et al., 2002; MacKinnon et al., 2004). In the case of continuous mediating variables with missing data, Monte Carlo integration with 500 integration points generated randomly was applied (Muthén and Muthén, 1998-2012). As recommended by Preacher and Hayes (2008), unstandardized regression coefficients (B) were computed. Separate saturated and unsaturated (regression coefficient corresponding to the direct effect fixed to zero to examine whether the effect between sex and the depressive subtypes was entirely mediated over the indirect variables) path models were computed. The models were compared using the Akaike information criterion (AIC; Akaike, 1987). All path analyses were adjusted for the influence of the socio-demographic covariates age and SES, age due to its known influence based on previous studies and SES based on its trend significance level in Table 1 ***ok like this or not plausible?***.

Path models were performed using Mplus version 7 for Macintosh (Muthén and Muthén, 1998-2012). Model coefficients for indirect effects were calculated by multiplying the unstandardized effects from M/S on DV with the unstandardized effects from IV on M/S using the MODEL CONSTRAINT command in Mplus. The resulting unstandardized coefficients are equivalent to those from the INDIRECT procedure. The unstandardized direct and indirect effects were exponentiated leading to the calculation of ORs and CI. All other analyses were computed by SPSS statistics version 20 for Macintosh (SPSS Inc., USA). The level of statistical significance for all tests was set at $p < 0.05$.

3. Results

The sociodemographic characteristics of the 1624 depressive subjects with a lifetime diagnosis of MDD aged from 35 to 66 years are presented below (Table 1). The frequencies of the MDD subtypes by sex were as follows: males: atypical: n=76 (13.5%), melancholic: n=141 (25.0%), combined: n=53 (9.4%), unspecified: n=293 (52.0%); females: atypical: n=180 (17.0%), melancholic: n=281, (26.5%), combined: n=145 (13.7%), unspecified: n=455 (42.9%). The four MDD subgroups significantly differed with regard to their frequencies/distributions of sex, age of onset of MDD, early and late anxiety disorders, BMI, subjective judgment of general childhood, emotion-orientated coping, paternal encouragement of freedom, and Neuroticism. Trend-level associations ($p \leq 0.10$) were observed for SES, paternal denial of autonomy, and maternal encouragement of freedom. BMI was significantly higher for men (mean = 25.55, SD = 3.70) than for women (mean = 24.21, SD = 4.65) (Mann-Whitney U-test; $Z = -8.74$, $p = < 0.001$, two-sided).

From these 1624 depressive subjects, n = 293 (18%) exhibited a current MDD while n = 1331 (82%) had a remitted MDD. In addition, n = 946 (58.3%) received some form of psychopharmacological treatment at baseline. The detailed pharmacological substances were as follows: antidepressant drugs n = 620 (38.2%), anxiolytics/sedative drugs n = 694 (42.7%), antimanic drugs n = 14 (0.9%), antipsychotic drugs n = 43 (2.6%), stimulant drugs n = 4 (0.2%), antiparkinson drugs n = 2 (0.1%). The frequencies for treatment with psychotropic drugs were n = 140 (54.7%) for atypical MDD, n = 289 (68.5%) for melancholic MDD, n = 150 (75.8%) for combined MDD, and n = 367 (49.1%) for unspecified MDD. A total of n = 1126 (69.4%) of all 1624 depressive subjects had consulted a healthcare professional for depression at the time of the assessment.

--Insert Table 1 about here--

The bivariate associations of the examined variables fulfilling the criteria of the Baron and Kenny (1986) procedure for mediation are reported in Table 2. Female sex was associated with a higher risk of early and late anxiety disorders, higher emotion-orientated coping, and a lower BMI and age of MDD onset. The model regressing the depressive subtypes on the M/S revealed that early anxiety disorders and high scores on emotion-orientated coping were associated to all three depressive subtypes: atypical, melancholic, and combined atypical-melancholic, compared to unspecified MDD. Late anxiety disorders and a low age of MDD onset were associated with the melancholic depression and combined subtypes only. In contrast, high BMI was specific for the atypical and combined atypical-melancholic depression subtypes. The bivariate direct effects between sex and depression subtypes yielded a significant, 1.50-fold higher risk for women belonging to the atypical depression subtype and a 1.72-fold higher risk for women manifesting combined atypical-melancholic depressive features compared to men.

--Insert Table 2 about here--

The ORs with 95% CIs of the direct and indirect effects of the final path model are depicted in Table 3. The significant direct effects between sex and both the atypical and combined atypical-melancholic depression subtypes remained significant in the multivariate path model, indicating a partial mediation. The assumption of full mediation was further rejected by the improved model fit indices in the saturated model (AIC= 35589.664) versus the unsaturated model (AIC= 35594.098). The detailed analyses of the specific direction of influence of the M/S variables based on the criteria of Baron and Kenny (1986) revealed that BMI acted as a suppression variable in both the atypical and combined depressive subtypes. Mediation effects were found with regard to early anxiety disorders (atypical and combined subtypes), late anxiety disorders (melancholic and combined subtypes), age of onset MDD (combined subtype), and emotion-orientated coping (atypical subtype) (four criteria of Baron and Kenny not shown). Figure 1 illustrates the unstandardized regression coefficients and standard errors of the final path model. The IV sex is displayed on the left side and the depression subtypes with the categories atypical, melancholic, and combined atypical-melancholic depression (reference: unspecified MDD) are

shown on the right side. The direct effects between sex and the three depression subtypes are displayed by the large, overarching arrows ($B = 0.444$; $B = 0.124$; $B = 0.437$ for the three subtypes). The five M/S are embedded in the middle, with short bent arrows denoting indirect effects from IV to DV over M/S and straight arrows illustrating direct effects between IV and M/S and M/S and DV, respectively. Equivalent signs of direct and indirect effects refer to M variables (early anxiety disorders, emotion-orientated coping, age of onset MDD). In contrast to the OR and CI, the unstandardized regression coefficients relating to late anxiety disorders only reached trend levels of significance. Opposite signs allow for conclusions about S variables, and confirm the above-mentioned findings about the S BMI.

--Insert Figure 1 about here--

--Insert Table 3 about here--

Additional exploratory analyses restricted to males revealed remarkable results (data not shown). Males with atypical depression showed a female-associated profile with high emotion-orientated coping and early anxiety disorders in comparison with males who revealed unspecified depression. Furthermore, males belonging to the atypical subtype exhibited lower substance use than those who suffered from unspecified depression.

4. Discussion

The present study is novel in contributing to the issue of the preponderance of women in atypical and combined atypical-melancholic MDD in that it identified several variables associated with both female sex and these two subtypes of depression, which could be mediators of the strong association between female sex and the atypical and combined atypical-melancholic MDD subtypes. Indeed, using a community-based sample of 1624 adults with MDD and path models revealed that early anxiety disorders, high emotion-orientated coping, and low age of MDD act as mediator variables, whereas high BMI suppressed the direct effect between sex and the atypical and combined depression subtypes. Our analyses differentiated that the previously found general mechanism explaining sex differences of overall MDD (such as early anxiety disorders, age of MDD onset, and emotion orientated coping) are also interrelated variables between sex and the atypical/combined atypical-melancholic depression subtypes and have the potential to distinguish these subtypes from the unspecified depressive subgroup. Furthermore, we demonstrated that the omission of BMI as an atypical/ combined atypical-melancholic subtype-specific variable leads to an underestimation of the true women to men ratio within the context of research using depression subtypes.

Pure forms of depressive subtypes are distinguishable by their comorbidity profile, which becomes apparent considering the mediating effect between early anxiety disorders and the atypical depression subtype versus late anxiety disorders and the melancholic depression subtype. Consequently we can conclude that the association of early anxiety disorders with the combined atypical-melancholic subtype mainly results from the atypical phenomenology, whereas the association between late anxiety disorders and the combined subtype rather results from melancholic features. Hence, the findings of Breslau (1998; 1995) partially attributing the overall MDD sex differences to prior anxiety disorders might apply more to the pure atypical/combined atypical-melancholic subtypes than to the pure melancholic depression subtype. The closer temporal co-occurrence of anxiety and melancholia/combined atypical-melancholic states could support previous studies showing that the female-associated anxious subtype (Clayton et al., 1991; Halbreich and Kahn, 2007) overlaps more strongly with melancholic features than with atypical symptoms (Rush, 2007).

In a previous study, the subgroup of subjects fluctuating between atypical and melancholic symptom profiles generally showed high rates of comorbidity, such as mania, panic disorder, simple phobia, bulimia, antisocial personality disorder, and substance use (Levitan et al., 1997). Comorbidity between mood and anxiety disorders indicates higher severity (Kaufman and Charney, 2000). In line with Levitan et al.'s (1997) findings, the subgroup with combined atypical-melancholic features yielded the highest relative frequencies of both early and late anxiety disorders and slightly higher substance use. This study is the first to demonstrate that early and late anxiety disorders (however, only around the borderline significance level) mediate the path between sex and this female-related severe depression subtype. Beyond its comorbidity profile, also the pronounced early age of onset of the combined atypical-melancholic depression subtype underlines its higher severity. Early age of onset has been shown to indicate severity in outpatients (Zisook et al., 2007), community samples (Kessler et al., 2001), and, with a focus on depression subtype-specific risk factors, in atypical depression (Angst et al., 2002). Angst et al. (2002) discovered that the effect of early age of onset on atypical depression disappeared when the analysis was controlled for sex, suggesting that these variables share common variance. Schuch et al. (2014) demonstrated that a younger age of MDD onset and a higher risk of atypical depression were more frequent among women compared to men. The current data further differentiate these findings by specifying the mediating effect of early age of onset in the association between sex and the severe, combined atypical-melancholic subtype, which is only detectable by a carefully assessed history of atypical and melancholic features. Moreover, comparing the depression subtypes with the undifferentiated subtype allows for a more detailed differentiation between the symptom-based depression subtypes. ***Last sentence necessary? And shall I also mention details such as information coping and BMI in our study compared to Schuch et al. (2014)?***

The association between emotion-orientated coping and the female-preponderant atypical depression (and, with a tendency for the combined atypical-melancholic depression subtype) corroborates findings of studies showing that emotion-orientated coping is more likely in women (Hildebrandt et al., 2003; Tamres et al., 2002). To the best of our knowledge, only one study to date examined whether symptom-

based depressive subtypes differ as regards coping styles (Ravindran et al., 2002). The authors found no differences between the atypical and typical (melancholic) depressive subgroups in depressed outpatients, contrary to their prediction. Possible explanations for the discrepant results to our study are the means of comparison (atypical versus typical (Ravindran et al., 2002)); comparison with unspecified depressives in the current study) and the different subtype classification based on the HAMD-D scale (Ravindran et al., 2002) versus DSM-based in the current paper. The question remains how the associations between sex, emotion-orientated coping and atypical depression can be explained. Emotion-orientated coping might rather be a severity/distress marker than a specific feature of the atypical depression subtype: both emotion-orientated coping (Ravindran et al., 2002; Roy-Byrne et al., 1992) and atypical depression (Angst et al., 2006; Angst et al., 2002) were associated with depression severity/distress, which in turn is more pronounced in women (Hildebrandt et al., 2003). Furthermore, high neuroticism scores, a personality trait which is more prevalent in women (Lynn and Martin, 1997), could partly explain the mediating influence of emotion-orientated coping. The overlap between sex and neuroticism was shown to account for some of the sex difference in coping in a meta-analysis (Tamres et al., 2002). Actually, the atypical and combined atypical-melancholic depressives exhibited the highest neuroticism scores in the current study, but an earlier study based on the same data also showed a significant, strong positive correlation between neuroticism and emotion-orientated coping (Perrin et al., 2014), which precluded the use of both variables in the current analyses. Because coping styles are learned behavioral patterns, the present finding provides a potential target for depression subtype-specific treatment, as claimed by Baumeister and Parker (2012). Once again, the usefulness of the differentiation of MDD into symptom-based depression subtypes becomes apparent.

The strong association between high BMI and atypical depression found in the present study is in agreement with previous empirical findings (Hasler et al., 2004; Kendler et al., 1996; Lamers et al., 2013; Levitan et al., 2012). In the available literature focusing on overall MDD, the correlation between depression and obesity was sometimes unequal between the sexes, e.g., inversely correlated in men, but not in women (Palinkas et al., 1996) or linked to obesity in women only (Andreyeva et al., 2007). We expanded this knowledge by specifying that BMI enhanced the predictive validity of female sex on the

atypical and combined atypical-melancholic depression subtypes by suppressing irrelevant variance. Some authors hypothesized that the high overlap of atypical depression and BMI might reflect operational artefacts, because the diagnostic criteria of both disorders comprise increased food intake (Angst et al., 2002; Hasler et al., 2004). We handled this artefact by excluding the redundant criterion in the definition of atypical depression. However, it cannot be excluded that the associations found between atypical depression and BMI merely represent epiphenomena, although this possibility was judged to be fairly unlikely (Lamers, 2013). Another study even demonstrated shared familial/genetic factors of these two disorders (Kendler et al., 1996). In any case, being overweight and exhibiting atypical depression have turned out to be stable characteristics (Hasler et al., 2004; Kendler et al., 1996; Lamers et al., 2012b; Nierenberg et al., 1996; Rodgers et al., 2014a) and obviously represent highly entwined constructs.

In contrast to some studies based on samples of in-/outpatients (Hildebrandt et al., 2003; Xiang et al., 2012), on prospective community samples (Angst et al., 2007; Rodgers et al., 2014a; Rodgers et al., 2014b), and mixed community-clinical samples (Schuch et al., 2014) showing a preponderance of men with melancholic depression, this sex-difference was not observed in the current study. Angst: DSM-IV specifier, wie PsyCoLaus; Hildebrand Subtypisierung auf Rating Scale basierend, kann also nicht am Instrument liegen. Xiang auch neu, ZInEP auch neu, kann also nicht an Kohorte liegen . Gründe???

The result pertaining to the atypical depressive subtype in men who actually displayed a female-related profile is remarkable. In line with this finding, low serum testosterone levels were detected in atypical depressive men in a recent preliminary study (Rodgers et al., 2015). The evidence that the subgroup of atypical depressed men display a risk profile commonly associated with female sex, which contrasted with the unspecified depressive subtype in men, might be of relevance for mental health care providers and requires further investigation.

Limitations

Before discussing the final conclusions, some limitations need mentioning. First, although path models imply a causal origin between predictor and dependent variable, our data are cross-sectional. Maxwell et al. (2011) demonstrated that cross-sectional estimates can either underestimate or overestimate longitudinal parameters. Therefore, the present study should be seen as a prelude for longitudinal research investigating this topic. However, derived from previous empirical evidence, depression mostly occurs secondarily to comorbid conditions (Hasegawa et al., 1991; Kessler, 2012; Schuckit et al., 1997; Wittchen et al., 2000), as postulated regarding anxiety disorders in the present path model??. Nevertheless, we do not have knowledge of the temporal ordering between the variables and there are several possible causal pathways as to how they might interrelate. For example, emotion-oriented coping and elevated BMI could be a consequence of atypical depression. With regard to the latter possibility, causality cannot be definitely disentangled in the literature either, and there is longitudinal evidence for obesity preceding (atypical) MDD (Faith et al., 2011), for the reverse (Lasserre et al., 2014) as well as for a reciprocal link (Luppino et al., 2010). With regard to the combined atypical-melancholic depressive subtype it is also not possible to establish the direction of the association with BMI using our cross-sectional analysis. Similar to the results demonstrated for the atypical depressive subtype (Lasserre et al., 2014), it is also theoretically possible that the combined atypical-melancholic depressive episode precedes high BMI. Second, we cannot rule out a potential bias resulting from the higher percentage of subjects with a lifetime diagnosis of MDD having a remitted MDD at time of assessment compared to those subjects with current MDD. A further bias might have resulted from the high percentage of psychopharmacologically treated subjects at assessment, potentially confounding the results concerning the BMI. However, with regard to the discrimination of depression subtypes, the BMI increase following the atypical depressive episode was shown to be independent of psychotropic drug treatment in the same data (Lasserre et al., 2014). Moreover, we showed that subjects of the melancholic subtype exhibited an even higher psychotropic drug consumption compared with the atypical depression subtype, despite the latter had the highest BMI. We consequently reasoned that the BMI was not severely biased by psychotropic drug intake in the present study. Third, with regard to sex-specific risk factors, not all previously found factors (Kendler and Gardner, 2014) were available in the current paper, and in view of the large number of studies carried out in the context of sex differences of MDD, the present study

makes no claim to completeness regarding the explored M/S variables. Fourth, recall of depressive symptoms over lifespan is incomplete and existing literature has shown that depressed mood symptoms are more readily recalled by women compared to men (Thompson et al., 2004). However, although we do not know to which degree specific atypical or melancholic symptoms are affected by incomplete recall, it is unlikely that this recall is linked to associated conditions such as anxiety disorders, coping or BMI, which indeed would induce bias. Fifth, no information related to avoidance strategy was available, despite the fact that this coping dimension was also judged to be relevant (Parker and Endler, 1992).

Conclusions

Notwithstanding these limitations, our study provides new insight into the complex interrelations between sex, the female-related atypical and combined atypical-melancholic depression subtypes and the associated general and specific risk factors by disentangling these associations into separate direct and indirect effects. Our analyses suggest that particularly in women intervention strategies focusing on changing emotion-focused coping patterns and treatment of anxiety disorders and early depression might contribute to the prevention of atypical and combined atypical-melancholic episodes. However, prospective data need to confirm the temporal relationship between the occurrence of emotion-focused coping patterns and anxiety disorders and the incidence of atypical and combined atypical-melancholic episodes.

Acknowledgements and **Role of funding sources**

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Table 1. Socio-demographic and clinical characteristics of subjects with MDD ($n=1624$)

Characteristic	MDD subtypes				<i>p</i> -value (two-tailed)	Overall MDD $n=1624$
	Atypical $n=256$	Melancholic $n=422$	Combined atypical- melancholic $n=198$	Unspecified $n=748$		
Sex n (%)					< 0.01 ^a	
<i>Male</i>	76 (29.7)	141 (33.4)	53 (26.8)	293 (39.2)		563 (34.7)
<i>Female</i>	180 (70.3)	281 (66.6)	145 (73.2)	455 (60.8)		1061 (65.3)
Age, years mean (SD)	48.1 (8.6)	49.1 (8.6)	49.1 (8.6)	49.2 (8.8)	0.320 ^b	49.0 (8.7)
Civil status n (%)					0.588 ^a	
<i>Single</i>	52 (20.3)	61 (14.5)	32 (16.2)	133 (17.8)		278 (17.1)
<i>Married</i>	128 (50.0)	208 (49.3)	104 (52.5)	379 (50.7)		819 (50.4)
<i>Separated/divorced</i>	68 (26.6)	137 (32.5)	54 (27.3)	205 (27.4)		464 (28.6)
<i>Widowed</i>	8 (3.1)	16 (3.8)	8 (4.0)	31 (4.1)		63 (3.9)
Living status n (%)					0.396 ^a	
<i>Alone</i>	79 (30.9)	121 (28.7)	61 (30.8)	233 (31.1)		494 (30.4)
<i>With family</i>	163 (63.7)	268 (63.5)	122 (61.6)	443 (59.2)		996 (61.3)
<i>With friends/apartment-sharing community</i>	12 (4.7)	27 (6.4)	14 (7.1)	67 (9.0)		120 (7.4)
<i>Other</i>	2 (0.8)	6 (1.4)	1 (0.5)	5 (0.7)		14 (0.9)

Education ¹ <i>n</i> (%)					0.275 ^a	
<i>n</i> =20 missing						
<i>Low</i>	140 (55.3)	219 (52.3)	106 (54.4)	378 (51.3)		843 (52.6)
<i>Medium</i>	73 (28.9)	106 (25.3)	56 (28.7)	195 (26.5)		430 (26.8)
<i>High</i>	40 (15.8)	94 (22.4)	33 (16.9)	164 (22.3)		331 (20.6)
Socio-economic status ²	3.3 (1.3)	3.4 (1.3)	3.2 (1.3)	3.4 (1.3)	0.081 ^b	
mean (SD)						
<i>n</i> =3 missing						
Nationality					0.785 ^a	
<i>Swiss</i>	189 (73.8)	307 (72.7)	140 (70.7)	531 (71.0)		1167 (71.9)
<i>other</i>	67 (26.2)	115 (27.3)	58 (29.3)	217 (29.0)		457 (28.1)
Migration					0.559 ^a	
<i>n</i> =508 missing						
<i>yes</i>	35 (19.3)	49 (16.4)	21 (15.8)	99 (19.7)		204 (18.3)
<i>no</i>	146 (80.7)	250 (83.6)	112 (84.2)	404 (80.3)		912 (81.7)
Age of onset MDD,	33.7 (13.5)	32.8 (12.2)	30.0 (12.6)	34.4 (12.6)	< 0.001 ^b	33.3 (12.7)
years						
mean (SD)						
<i>n</i> =2 missing						
Early anxiety disorders ³	114 (44.5)	173 (41.0)	98 (49.5)	258 (34.5)	< 0.001 ^a	643 (39.6)
Late anxiety disorders ⁴	34 (13.3)	68 (16.1)	43 (21.7)	74 (9.9)	< 0.001 ^a	219 (13.5)
Substance use ⁵	31 (12.1)	74 (17.5)	36 (18.2)	126 (16.8)	0.222 ^a	267 (16.4)
Body Mass Index	26.07 (4.80)	24.12 (4.04)	25.16 (5.14)	24.38 (4.10)	< 0.001 ^b	24.7 (4.4)

mean (SD)						
<i>n</i> =2 missing						
General childhood ⁶	1.6 (0.8)	1.6 (0.8)	1.7 (0.9)	1.5 (0.7)	< 0.01 ^b	1.6 (0.8)
<i>n</i> =1 missing						
Coping						
<i>n</i> =531 missing						
<i>Emotion-orientated coping</i>	10.3 (3.9)	9.7 (3.9)	10.3 (3.7)	9.1 (3.7)	< 0.001 ^b	9.6 (3.8)
<i>Problem-orientated coping</i>	7.8 (1.7)	7.6 (2.0)	7.6 (1.9)	7.7 (1.7)	0.733 ^b	7.7 (1.8)
<i>Help-seeking behaviour</i>	4.8 (2.7)	4.7 (2.5)	4.5 (2.5)	4.4 (2.7)	0.243 ^b	4.5 (2.6)
Parental Bonding						
<i>Mother: care</i>	23.6 (9.1)	23.0 (9.5)	22.4 (9.2)	24.1 (9.1)	0.164 ^b	23.5 (9.2)
<i>n</i> =518 missing						
<i>Father: care</i>	21.8 (9.3)	20.8 (9.0)	20.4 (9.6)	21.0 (8.8)	0.569 ^b	21.0 (9.0)
<i>n</i> =566 missing						
<i>Mother: denial of autonomy</i>	7.0 (4.6)	6.7 (4.8)	7.3 (4.9)	6.6 (4.4)	0.445 ^b	6.8 (4.6)
<i>n</i> =518 missing						
<i>Father: denial of autonomy</i>	5.2 (3.8)	5.6 (4.1)	4.7 (3.3)	4.8 (3.8)	0.081 ^b	5.0 (3.9)
<i>n</i> =566 missing						
<i>Mother: encouragement of freedom</i>	9.6 (4.6)	9.2 (4.4)	8.5 (4.1)	9.5 (4.4)	0.071 ^b	9.3 (4.4)

n=518 missing

Father: encouragement of freedom 9.8 (4.5) 9.1 (4.3) 8.5 (4.4) 9.5 (4.6) < 0.05^b 9.3 (4.5)

n=566 missing

Personality traits

Neuroticism 12.9 (5.3) 12.1 (5.5) 13.5 (5.2) 10.6 (5.4) < 0.001^b 11.7 (5.5)

n=496 missing

Extraversion 10.2 (4.6) 10.4 (4.6) 10.0 (5.0) 10.6 (4.6) 0.529^b 10.4 (4.7)

n=496 missing

Psychoticism 3.2 (2.2) 3.2 (2.3) 3.3 (2.2) 3.2 (2.2) 0.724^b 3.2 (2.2)

n=496 missing

MDD, Major Depressive Disorder

SD, standard deviation

^a Chi-Square test/Fisher-test.

^b Kruskal–Wallis test.

¹ low: compulsory education, apprenticeship/vocational school; medium: preparatory school for general qualification for university entrance, vocational education, vocational secondary school/intermediate diploma school; high: university/university of applied science.

² Socio-economic status following Hollingshead's index: A value of 3 represents an SES of III (middle class).

³ Simple phobia, social phobia, separation anxiety disorder, overanxious disorder

⁴ Panic disorder, generalized anxiety disorder, agoraphobia

⁵ Alcohol/ drug abuse/dependence

⁶ Rated on a Likert Scale ranging from 1 (happy) to 4 (very unhappy)

Table 2. Bivariate results of variables meeting the mediator criteria according to Baron and Kenny (1986), adjusted for age and socio-economic status ($n=1621$)

cave: $n=1$ atypical und $n=3$ unspecified go lost because of missings of SES; regarding BMI $n=2$ additional because of $n=1$ missing in melancholic ST and $n=1$ in mixed ST; regarding age of onset $n=2$ additional because of missing in melancholic ST

Sex	Mediator (M)	Associations between sex and M	Associations between M and depression subtypes (reference: unspecified depression)			Direct associations between sex and depression subtypes (reference: unspecified depression)		
		Estimate	Estimate			Estimate		
Female sex	Early anxiety disorders ¹	1.86 (1.61-2.15)*** ³	Atypical DST 1.48 (1.11-1.98)** ³	Melancholic DST 1.31 (1.03-1.68)* ³	Mixed atypical-melancholic DST 1.84 (1.34-2.53)*** ³	Atypical DST 1.50 (1.10-2.04)** ³	Melancholic DST 1.27 (0.99-1.64) ³	Mixed atypical-melancholic DST 1.72 (1.21-2.44)*** ³
	Late anxiety disorders ¹	2.19 (1.71-2.81)*** ³	Atypical DST 1.32 (0.85-2.05) ³	Melancholic DST 1.73 (1.21-2.46)*** ³	Mixed atypical-melancholic DST 2.46 (1.63-3.73)*** ³			
	Body Mass Index	737.43; 950.83, $p<0.001$ ²	Atypical DST 1.09 (1.05-1.12)*** ³	Melancholic DST 0.98 (0.95-1.01) ³	Mixed atypical-melancholic DST 1.04 (1.01-1.08)* ³			
	Age of MDD onset	790.64; 850.85, $p<0.01$ ²	Atypical DST 1.00 (0.99-1.01) ³	Melancholic DST 0.99 (0.98-1.00)* ³	Mixed atypical-melancholic DST 0.97 (0.96-0.98)*** ³			
	Emotion oriented coping	586.21; 464.81, $p<0.001$ ²	Atypical DST 1.08 (1.03-1.13)*** ³	Melancholic DST 1.05 (1.00-1.09)* ³	Mixed atypical-melancholic DST 1.08 (1.02-1.14)*** ³			

DST, Depression subtype; MDD, Major Depressive Disorder

¹ Early anxiety disorders: simple phobia, social phobia, separation anxiety disorder, overanxious disorder; late anxiety disorders: panic disorder, generalized anxiety disorder, agoraphobia

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²Odds ratio (OR) with 95% confidence intervals (CI)

*p<.05

**p<.01

***p<.001

References

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Table 3. Results of the path model examining the direct and indirect effects of sex on the depressive subtypes ($n=1621$) via mediation/suppression variables

Sex	Mediator (M)	Indirect associations Sex → M → depression subtypes			Direct association of sex and depression subtypes		
		OR (95% CI)			OR (95% CI)		
Female sex	Early anxiety disorders	Atypical DST 1.43 (1.05-1.94)*	Melancholic DST 1.16 (0.89-1.49)	Mixed atypical-melancholic DST 1.43 (1.02-2.00)*	Atypical DST 1.56 (1.12-2.16)**	Melancholic DST 1.13 (0.87-1.48)	Mixed atypical-melancholic DST 1.55 (1.07-2.24)*
	Late anxiety disorders	Atypical DST 1.15 (0.73-1.81)	Melancholic DST 1.60 (1.11-2.29)*	Mixed atypical-melancholic DST 2.01 (1.31-3.10)**			
	Body Mass Index	Atypical DST 1.10 (1.06-1.13)**	Melancholic DST 0.99 (0.96-1.02)	Mixed atypical-melancholic DST 1.05 (1.01-1.09)**			
	Age of MDD onset	Atypical DST 1.01 (0.99-1.02)	Melancholic DST 0.99 (0.98-1.00) sig?	Mixed atypical-melancholic DST 0.98 (0.96-0.99)**			
	Emotion-orientated coping	Atypical DST 1.06 (1.01-1.11)*	Melancholic DST 1.04 (0.99-1.08)	Mixed atypical-melancholic DST 1.05 (1.00-1.11) sig?			

All model estimates are adjusted for age and socio-economic status

Discrepancy to total number of subjects with MDD resulted from $n=3$ missing items.

* $p < .05$
 ** $p < .01$