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Childhood maltreatment and impact on clinical features of major depression in adults

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ABSTRACT

Objectives: This study examined: 1) the prevalence of childhood maltreatment (CMT) in individuals with chronic and/or recurrent depression, 2) the association between CMT and depressive symptoms, 3) the link between CMT and worse clinical presentation of depression, 4) the effects of accumulation of different types of CMT, and 5) the relationship between the age at CMT and depression.

Methods: We analyzed the baseline data of 663 individuals from the CO-MED study. CMT was determined by a brief self-reported questionnaire assessing sexual abuse, emotional abuse, physical abuse, and neglect. Correlational analyses were conducted.

Results: Half of the sample (n = 331) reported CMT. Those with CMT had higher rates of panic/phobic, cognitive and anhedonic symptoms than those without CMT. All individual types of maltreatment were associated with a poorer clinical presentation including: 1) earlier MDD onset; 2) more severe MDD, 3) more suiccidality, 4) worse quality of life, and functioning, and 5) more psychiatric comorbidities. Clinical presentation was worse in participants who reported multiple types of CMT.

Conclusions: In chronic and/or recurrent depression, CMT is common, usually of multiple types and is associated with a worse clinical presentation in MDD. The combination of multiple types of CMT is associated with more impairment.

**CO-MED study:* Combining Medications to Enhance Depression Outcomes (clinicaltrial.gov identifier NCT00590863).

1. Introduction

Childhood maltreatment (CMT) - also referred to as early life stress or childhood trauma - is one of the most significant risk factors for the development of major depressive disorder (MDD).(APA, 2013; Dunn et al., 2013; Heim and Binder, 2012; Leeb and National Center for Injury Prevention and Control (U.S.). 2008; Li et al., 2016; Mandelli et al., 2015; Nanni et al., 2012; Otte et al., 2016) For example, a study of 2215 adults aged 18 to 93 years-old that assessed the strength of the association between 19 well-established risk factors for MDD, and MDD diagnosis found that CMT had the fifth strongest association with MDD among all 19 risk factors.(Schaakxs et al., 2017) Similarly, a longitudinal study that followed more than 10,000 individuals for one year observed that physical/emotional CMT and sexual CMT were both among the top 13 of 39 risk factors for developing MDD, with hazard ratios of 2.68 (95% confidence interval – CI: 2.26–3.18), and 2.57 (95% CI 2.01–3.30), respectively.(Bottomley et al., 2010) Overall, individuals who report CMT have a two- to four-fold greater risk of developing MDD(Heim and Binder, 2012) than those without such history, and the risk increases with multiple types of CMT.(APA, 2013; Heim and Binder, 2012) The increase in prevalence of MDD with exposure to CMT

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has been observed in clinical, epidemiological, and twin studies conducted in several countries.(Heim and Binder, 2012; Nanni et al., 2012; Schulz et al., 2014) Adults with MDD and CMT have worse clinical presentation than persons with MDD but no CMT including earlier onset of MDD,(Goldberg et al., 2019; Klein et al., 2009; Nelson et al., 2017b; Tunnard et al., 2014; Widom et al., 2007) and more severe depressive symptoms.(Edwards et al., 2003; Kim et al., 2013; Klein et al., 2009; Negele et al., 2015). There seems to be a dose-response relationship between the severity of the CMT experiences and worse clinical presentation of MDD.(Chapman et al., 2004; Li et al., 2016; Nanni et al., 2012)

The Centers for Disease Control and Prevention (CDC) describes four main types of CMT: sexual abuse, emotional (psychological) abuse, physical abuse, and neglect.(Leeb and National Center for Injury Prevention and Control (U.S.). 2008) Sexual, emotional and physical abuse are acts of commission, i.e. active and intentional acts or words that harm, threaten to harm or may potentially harm a child. In sexual abuse, the deliberate act consists of any attempted or completed sexual contact or act, or exploitation via sexual interaction without direct contact of a child by a caregiver including exposure to pornography, sexual films, sexual harassment, sexual trafficking or prostitution. Emotional abuse occurs when a caregiver intentionally mentions to a child that he/she is endangered, unwanted, unloved, flawed or worthless and may be manifested in behaviors such as isolating, terrorizing, intimidating or denigrating. Physical abuse is described as the deliberate use of "physical force against a child that results in, or has the potential to result in, physical injury" including punching, kicking, burning, hitting, and other behaviors. Neglect, on the other hand, is not an act of commission (active) but an act of omission where the caregiver does not provide for the child's basic needs such as hygiene, nutrition, emotional support, education and access to medical care. (Leeb and National Center for Injury Prevention and Control (U.S.). 2008)

However, there remain other questions regarding the relationship between CMT and clinical features of depressed individuals. First, it is not clear how distinct kinds of CMT relate to each other (i.e. do they frequently co-occur? are there types that are rarely found as single experiences while others are more common as independent events?). Second, it is also unclear if any specific depressive symptoms are more common in individuals with a history of maltreatment compared to those without a history. For instance, when compared to individuals with MDD without a history of CMT, individuals with MDD with a history of CMT has been linked to both increased and decreased appetite, sleep and psychomotor activity,(Bader et al., 2007; Carli et al., 2011; Levitan et al., 1998; Withers et al., 2013) while other studies have failed to observe any association of CMT with changes in these neurovegetative symptoms.(Vares et al., 2015) Similar inconsistency has been seen with the presence of greater cognitive impairment (Vares et al., 2015) and higher risk of suicidal behavior (Dube et al., 2001; Goldberg et al., 2019; Kim et al., 2013; Klein et al., 2009; Martins et al., 2014). Understanding how CMT is related to the symptomatic presentation of MDD might provide important hints about underlying pathophysiology and may help the development of more customized treatments for maltreated individuals with MDD. Third, despite the difficulties of disentangling the different types of abuse (i.e. usually there is a significant overlap of occurrence between them), the strength of the association between distinct types of CMT and MDD needs to be further understood. Fourth, the impact of the accumulation of multiple kinds of CMT, specifically in chronic and/or recurrent MDD, requires further examination. In addition, the age at which CMT occurs is a key variable (Dunn et al., 2013; Gomez et al., 2017) but it has not frequently been examined in all studies, thus there is a need to clarify the relationship between age at which CMT happened and worse clinical characteristics in MDD, such as greater symptom severity, greater overall impairment, and higher rates of chronic and/or recurrent MDD. Deeper understanding of these factors may also better guide preventive care, acute interventions (immediately after the occurrence of maltreatment) and longer-term management of MDD in the context of CMT.

Another aim of this research is to clarify the relationship between number of types of CMT and age at CMT, and worse features specifically in chronic and/or recurrent MDD. Despite a recent negative study, (van Dijk et al., 2019) most of the available literature suggests that the accumulation of different types of CMT is associated with poorer clinical characteristics in MDD(APA, 2013; Heim and Binder, 2012; McCutcheon et al., 2009; Negele et al., 2015; Nelson et al., 2017b; Wainwright and Surtees, 2002). As might be expected, some other psychiatric disorders including psychotic disorders, bipolar disorder, panic disorder and trauma-related disorders show worse clinical presentation in the setting of CMT.(Briere et al., 2008; Copeland et al., 2018; Myers et al., 2015) However, some studies have failed to show a link between heavier load of CMT and frequency and/or severity of some specific diagnoses such as generalized anxiety disorder, social anxiety disorder, some types of substance use disorders, and attention-deficit/hyperactivity disorder.(Copeland et al., 2018; Nelson et al., 2002; Zlotnick et al., 2008). In addition, few studies have examined CMT in chronic and/or recurrent MDD, which can be challenging to manage effectively(Hölzel et al., 2011).

In addition, the relationship between age at CMT and the negative consequences in psychopathology is unclear. Some studies suggest that CMT older children are more prone to suffer negative consequences of CMT because they have greater cognitive skills and, therefore, can fully appreciate the meaning of CMT.(Gomez et al., 2017) For example, Gomez and colleagues (2018) investigated the impact of age of CMT and suicidal behavior in a nationally-representative sample of 9272 adolescents. The authors found that individuals with CMT between ages six and ten had more suicidal ideation, suicide plan and previous suicide attempts than those who suffered CMT before age six. (Gomez et al., 2017) On the other hand, CMT in early ages might be closely associated with higher risk of long-lasting negative consequences in mental health since several functional and structural brain changes happen early in the child development. For instance, Dunn and collaborators (2017) found that adults who were maltreated between ages zero and five had a higher risk of developing MDD than adults who had CMT after age five.(Dunn et al., 2013) Similarly, Hambrick et al. (2019) observed that children exposed to stressful situations at early childhood (before age four) were at higher risk of poorer mental health outcomes than children maltreated in later ages. (Hambrick et al., 2019)

A large proportion of the socioeconomic burden associated with MDD comes from its chronicity and recurrence.(Burcusa and Iacono, 2007) Depressive episodes are not distributed homogeneously in the population and they cluster in some individuals who have a poor longitudinal course and several episodes of MDD over their lifetime. (Burcusa and Iacono, 2007; Nanni et al., 2012). A robust literature (summarized in two recent meta-analyses) show that CMT is a risk factor for chronic and/or recurrent MDD. (Klein et al., 2009; Nanni et al., 2012; Negele et al., 2015; Nelson et al., 2017b; Wiersma et al., 2009) However, there is a relative paucity of studies on CMT in individuals with chronic and/or recurrent depression. (Nanni et al., 2012) Therefore, further investigation of CMT in a sample of chronic and/or recurrent MDD may provide important insights about factors that are associated with persistence and relapse of MDD.

We conducted secondary analyses with the baseline data from the Combining Medications to Enhance Depression Outcomes (CO-MED) study, a large trial that enrolled 665 in-episode individuals (663 assessed for CMT) with chronic and/or recurrent MDD. We sought to clarify the following:

1) How do different types of CMT relate to each other in MDD?
2) Does any history of CMT associate with specific symptoms of MDD?
3) Which types of CMT are associated with worse clinical characteristics of MDD?

4) Do individuals with a history of multiple types of CMT have worse clinical characteristics of MDD than individuals with fewer different types of CMT?
5) Do individuals for whom CMT occurred at an earlier age have worse clinical characteristics than individuals who suffered CMT at a later age?

We hypothesized that CMT would be common and that there would be a substantial overlap of occurrence between different types of CMT. We also expected that participants who reported a history of CMT would likely have higher rates of anxious and avoidant symptoms and present an overall worse clinical presentation (including greater symptom severity, greater overall impairment, and higher rates of chronic and/or recurrent MDD.) than participants who did not report a history of CMT. As previous research observed that emotional abuse and neglect had more robust associations to development of MDD than other types of CMT,(Nelson et al., 2017b) we hypothesized that these two types of maltreatment would have a stronger relationship to worse clinical characteristics of MDD than sexual and physical abuse. Finally, we expected that participants with multiple types of CMT and with CMT occurring at a younger age would have more severe psychopathology and impairment than those with fewer types of maltreatment or CMT at older age, respectively.

2. Method

2.1. Sample

The CO-MED study (clinicaltrial.gov identifier NCT00590863) was a randomized clinical trial that enlisted 665 outpatients with non-psychotic in-episode MDD from six primary care and nine psychiatric clinics between March 2008 and September 2009. Eligible participants met criteria for recurrent (more than one episode with current episode lasting 2 or more months) and/or chronic (current episode lasting at least 2 years) MDD as established by clinical interview and an additional DSM-IV symptom checklist, based on the Mini-International Neuropsychiatric interview (MINI),(Sheehan et al., 1998) completed by a research coordinator.(Rush et al., 2011) Participants were aged between 18 and 75 years, scored at least 16 on the 17-item Hamilton Depression Rating Scale (HAM-D_{17}),(Hamilton, 1960) and were not taking psychotropic medications at the time of enrollment. Participants were excluded for: 1) any psychotic illness, 2) lifetime diagnosis of bipolar disorder, 3) current diagnosis of substance use disorder, and 4) need for hospitalization or medical conditions that impeded the safe use of the studied medications.

2.2. Ethics

CO-MED was approved by the Institutional Review Boards at UT Southwestern Medical Center (Dallas, TX), the University of Pittsburgh Data Coordinating Center (Pittsburgh, PA), all participating regional centers and relevant clinics. Informed consent was collected from all individuals.

2.3. Assessment of childhood maltreatment (CMT)

In order to assess CMT, we developed a very brief self-reported questionnaire. We elaborated a straightforward, quickly answerable, and simple to score and interpret 4-item instrument. This brevity does not allow more detailed and sensitive evaluation of childhood trauma; however, there is robust evidence that a short and focused instrument is easier to implement in real clinical settings,(Beidas et al., 2015; Irving et al., 2017; Jensen-Doss A, 2010; Unutzer and Park, 2012) potentially attenuating the burdensome paperwork that patients and providers are required to complete.(Kumar, 2007)

We used “yes-or-no” questions since it is overall faster and easier to answer than other more formats.(Brink et al., 1982) Our questionnaire investigated CMT based on the CDC definition of different types of CMT (i.e., sexual abuse, emotional abuse, physical abuse, and neglect). We also applied the CDC definition of “child”, which is anyone aged less than 18 years of age.(Leeb and National Center for Injury Prevention and Control (U.S.). 2008) Participants answered the questionnaire at baseline, which consisted of four focused yes-or-no questions (Supplemental Table 1).

2.4. Clinical measurements

MDD Characteristics and Depressive Symptoms: Age at MDD onset, number of previous episodes, duration of current episode and previous suicide attempts were assessed during the MINI interview. The 30-item Inventory of Depressive Symptomatology - Clinician Version (IDS-C) (Rush et al., 1996) was used to evaluate current suicidal ideation (score of at least 1 on question 18), melancholic features, and atypical features.(Rush et al., 2011)

Psychiatric Comorbidities: Current prevalence of psychiatric comorbidities was evaluated with the 125-item Psychiatric Self-Administered Diagnostic Screening Questionnaire.(Rush et al., 2005; Zimmerman and Sheeran, 2003)

MDD Severity: MDD severity was assessed using the 17-item Hamilton Depression Rating Scale (HAM-D_{17}), the IDS-C from which the 16-item Quick Inventory of Depressive Symptomatology – Clinician Rated (QIDS-C) (Rush et al., 2003) was obtained, and the 16-item Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR). (Rush et al., 2003) All severity questionnaires assessed MDD symptoms in the past week.

Overall Impairment: Quality of life was evaluated with the 32-item self-administered Quality of Life Inventory (QOLI).(Frisch et al., 2005) QOLI uses a 3-point rating scale and covers 16 different life domains. Higher scores in the QOLI equate to better levels of quality of life. (Frisch et al., 2005) The 5-item self-administered Work and Social Adjustment Scale (WSAS) assessed social adjustment impairment. (Mundt et al., 2002) The 5 items are anchored from 0 to 8 and greater scores mean higher impairment. WSAS investigated five areas: work, home management, social leisure activities, private leisure activities, and close relationships. Medical comorbidities were assessed with the 36-item self-reported Comorbidity Questionnaire.(Sangha et al., 2003)

2.5. Statistics

Categorical data were summarized as frequency and percentages while continuous variables were summarized as mean and standard deviations (SD). Chi-Square tests and independent sample Student's t-tests were conducted to identify demographic and clinical characteristics that were substantially different between participants who reported and participants who did not report CMT. Cohen's d was provided. Based on the cut-offs reported by Cohen,(Cohen, 1988) $d \geq 0.65$ was considered a large effect size, $0.10 \leq d < 0.35$ was considered a small effect size and $0.35 \leq d < 0.65$ was classified a medium effect size.

We addressed if individuals exposed to multiple different types of CMT have worse clinical characteristics of MDD than individuals with fewer different types of CMT. We used the Cochran-Armitage test to assess if the occurrence of more types of CMT were associated with higher (or lower) proportions of categorical demographic or clinical characteristics. Linear trend tests in mean were used to assess such trends in terms of continuous demographic or clinical characteristics. To investigate if persons who were exposed to CMT at earlier age had worse clinical characteristics that those were exposed to CMT at older age, we divided the individuals with any CMT in a group who suffered CMT before age 10 (latency phase) and another group who suffered CMT at age 10 or later (adolescence). This classification is consistent with previous work.(Collishaw et al., 2007) Cochran-Armitage and

Table 1
Demographics and clinical variables in individuals with major depressive disorder (MDD), according to history of childhood maltreatment (CMT) (N = 663).

Variables	No CMT n = 332	Any CMT n = 331	Effect Size[a]
DEMOGRAPHICS			
Categorical Variables	(%)	(%)	Cohen's d
Female gender	65%	71%	0.14*
White race	64%	64%	0.01
Hispanic ethnicity	15%	15%	0.01
Continuous Variables	Mean (SD)	Mean (SD)	Cohen's d
Age	44.2 (13.0)	41.3 (12.9)	0.22*
Years of education	13.8 (2.8)	13.8 (3.2)	0.00
Body mass index	31.1 (8.4)	31.0 (9.2)	0.01
CLINICAL VARIABLES			
Categorical Variables	(%)	(%)	Cohen's d
MDD Characteristics			
Onset of MDD before age 18 (MINI)	29%	60%	0.64**
Chronic MDD (at least 2 years of duration)	51%	60%	0.18*
Recurrent MDD (at least 2 MDD episodes)	80%	76%	0.10*
Chronic AND recurrent MDD	31%	36%	0.10*
Current suicidal ideation (IDS-C)	52%	67%	0.31*
Previous suicidal attempts (MINI)	5%	13%	0.27*
Atypical features (IDS-C)	10%	21%	0.31*
Melancholic features (IDS-C)	30%	38%	0.16*
Psychiatric Comorbidities[b]			
Agoraphobia	6%	15%	0.27*
Alcohol abuse	9%	11%	0.07
Bulimia	9%	14%	0.15*
Generalized anxiety disorder	15%	24%	0.22*
Obsessive-compulsive disorder	10%	14%	0.14*
Panic disorder	8%	12%	0.13*
Post-traumatic stress disorder	9%	16%	0.21*
Social phobia	21%	32%	0.25*
Continuous Variables	Mean (SD)	Mean (SD)	Cohen's d
MDD Characteristics			
Age at onset (MINI)	28.8 (14.3)	19.2 (12.2)	0.72***
Number of previous MDD episodes (n = 507)	7.4 (13.8)	20.6 (69.2)	0.26*
Duration of current MDD episode	47.8 (86.0)	76.0 (119.5)	0.27*
MDD Severity			
QIDS-SR	14.5 (4.2)	16.4 (4.1)	0.46**
QIDS-C	15.2 (3.4)	16.4 (3.4)	0.35**
IDS-C	36.7 (8.9)	40.3 (9.1)	0.40**
HAM-D_{17}	23.3 (4.7)	24.4 (4.8)	0.23*
Overall Impairment			
Quality of life (QOLI)	24.4 (13.5)	17.6 (13.7)	0.50**
Work and social impairment (WSAS)	25.3 (9.1)	28.6 (8.2)	0.38**
Number of psychiatric comorbidities (PDSQ)	1.0 (1.5)	1.5 (1.7)	0.31*
Number of medical comorbidities	1.9 (1.5)	2.0 (1.6)	0.06

[a] Effect size (EF): * = small (0.10 ≤ EF < 0.35); ** = medium (0.35 ≤ EF < 0.65); *** = large (0.65 ≤ EF). [b] For psychiatric comorbidities, data were presented in the table only if the disorder had a prevalence of at least 10% in the total sample. SD = Standard deviation. Bold = medium or large effect size.

linear trend tests were used to assess if there was a trend to have worse MDD features in people with early CMT or late CMT.

We used false discovery rate to adjust p values for multiple comparisons. All analyses were done using SAS 9.4 (SAS Inc, Cary, NC).

3. Results

3.1. Description of the sample

The sociodemographic and clinical characteristics of participants stratified by the presence of any CMT are shown in Table 1. Two-thirds of the sample were female (68%, n = 451) and the mean age was in the early forties (mean = 42.76, SD = 12.98). Slightly more than half of the participants (55%, n = 367) had chronic MDD and approximately three-fourths (78%, n = 515) had recurrent MDD.

Approximately half of the sample (50%, n = 331) reported some type of CMT. The rates for specific maltreatment types were 22% (n = 145) for sexual abuse, 39% (n = 261) for emotional abuse, 20% (n = 131) for physical abuse and 36% (n = 240) for neglect. Fig. 1 displays the prevalence of all possible combinations of the different types of CMT. The mean age for specific types of CMT ranged from 7.2 [standard deviation (SD) = 4.2] for neglect, to 9.0 (SD = 4.0) for sexual abuse (Supplemental Figure 1).

3.2. Relationship between any CMT and sample characteristics

Chi-Square tests and independent Student's t-tests found that any history of CMT (independent of type or number), was associated with earlier MDD onset, higher rates of current suicidal ideation, greater number of previous suicide attempts, worse MDD severity, poorer quality of life, and greater work and social impairment (Table 1). For all these associations, effect sizes using Cohen's d were at least moderate.

1) **How do different types of CMT relate to each other in MDD?**

There was a substantial overlap of occurrence between different types of CMT. Just one quarter (25.6%) of the individuals with history of CMT reported experiencing only one type (Table 2). Physical abuse rarely occurred alone. Virtually all individuals with history of physical abuse (98%) had a co-occurring CMT (96% had emotional abuse, while 81% had neglect).

The mean number of types of CMT was 2.8 (SD = 1.2) for sexual abuse (i.e., besides sexual abuse they had in average 1.8 other types of CMT), 2.7 (SD = 1.0) for emotional abuse, 3.3 (SD = 0.8) for physical abuse and 2.7 (SD = 0.9) for neglect.

1) **Does any history of CMT associate with specific symptoms of MDD?**

Chi-Square tests and independent sample Student's t-tests individuals with any history of CMT (independent of type or number) reported higher rates of panic/phobic, cognitive and anhedonic symptoms (impaired capacity for pleasure, impaired mood reactivity and general interest) than individuals without history of CMT (Supplemental Table 2). Effect sizes for these symptoms were small (Cohen's d between 0.24 and 0.32).

1) **Which types of CMT are associated with worse clinical characteristics of MDD?**

All types of CMT were associated with worse MDD severity, poorer quality of life, more work and social impairment, and increased psychiatric comorbidity. The effect sizes of the different kinds of CMT in the MDD severity scales (QIDS-SR, QIDS-C, IDS-C and HAM-D17) were similar. They ranged from 0.24 to 0.46 for sexual abuse, from 0.29 to 0.47 for emotional abuse, from 0.32 to 0.40 for physical abuse and from 0.22 to 0.44 for neglect.

Regarding type-specific relationships, sexual abuse was much more prevalent in women. Effect sizes showed that emotional abuse had the strongest associations with early onset of MDD (Cohen's d = 0.68) and worse quality of life (Cohen's d = 0.47) (Table 3).

1) **Do individuals with a history of multiple types of CMT have worse clinical characteristics of MDD than individuals with fewer different types of CMT?**

Cochran-Armitage tests and linear trend tests revealed that there was association between higher number of types of CMT and worse clinical presentation (Table 4). The associations with earlier onset, suicidal behavior, worse severity of depression, more functional

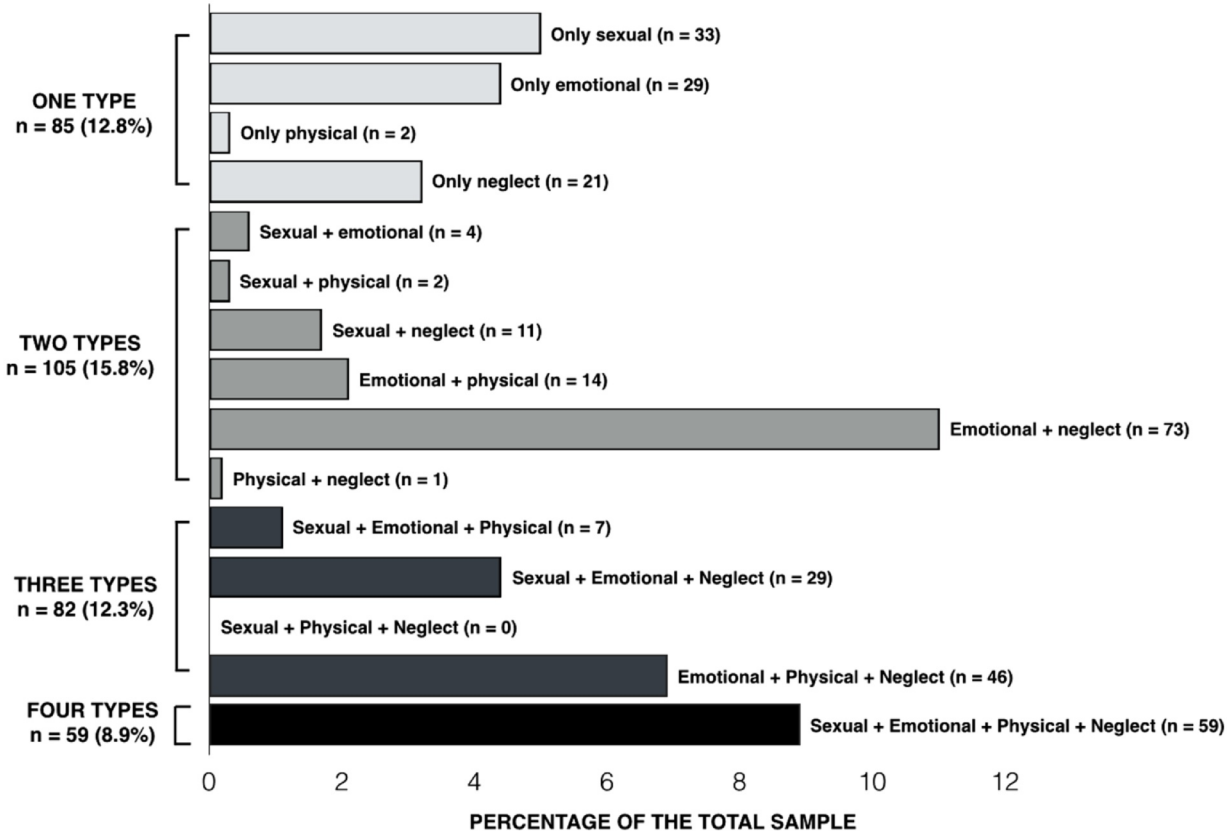

Fig. 1. Prevalence of sexual abuse, emotional abuse, physical abuse and neglect in individuals with major depressive disorder (N = 663).

Table 2
Co-occurrence of different types of childhood maltreatment (CMT) in individuals with major depressive disorder (N = 663).

Variables	Type of CMT Sexual Abuse n = 145	Emotional Abuse n = 261	Physical Abuse n = 131	Neglect n = 240
Type of CMT	(%)	(%)	(%)	(%)
Sexual abuse	NA	38%	52%	41%
Emotional abuse	68%	NA	96%	86%
Physical abuse	47%	48%	NA	44%
Neglect	68%	79%	81%	NA
Cumulative Number of CMT[a]	(%)	(%)	(%)	(%)
One type (no co-occurring CMT)	23%	11%	2%	9%
Two types	12%	35%	13%	35%
Three types	25%	31%	41%	31%
Four types	41%	23%	45%	25%

[a] Cumulative Number of CMT = total number of different types of childhood maltreatment. Four different types were assessed: sexual abuse, emotional abuse, physical abuse and neglect. NA = not applicable.

impairment and more psychiatric comorbidities showed a high statistical significance (p < .001).

1) **Do individuals for whom CMT occurred at an earlier age have worse clinical characteristics than individuals who suffered CMT at a later age?**

No. Cochran-Armitage tests and linear trend tests showed no statistically significant clinical differences in those who experienced any CMT before age 10 compared to those who suffered any CMT at age 10 or later (Supplemental Table 3).

4. Discussion

This study aimed to better understand the relationship between CMT and MDD clinical presentation by conducting secondary analyses in a sample of 663 treatment-seeking individuals with chronic and/or recurrent depression.

Our main findings were: 1) the experience of CMT was common, and multiple kinds of CMT usually co-occurred; 2) a history of CMT was associated with higher rates of panic/phobic, cognitive and anhedonic symptoms; 3) all types of CMT were associated with earlier MDD onset, more severe MDD, more suicidal behavior, worse quality of life, poorer work and social adjustment, and more psychiatric comorbidities, 4) experience of a greater number of types of CMT was associated with worse clinical characteristics than having a history of fewer types of CMT, and 5) individuals for whom CMT occurred at an earlier age had no statistically significant different clinical characteristics compared to individuals who experienced CMT at a later age.

Half of our sample had CMT, the most common types were emotional abuse and neglect, and different types usually co-occurred. These findings are consistent with previous literature. A recent large meta-analysis, which assessed similar CMT categories to our study, in individuals with MDD found that 46% of them had at least one kind of CMT.(Nelson et al., 2017b) A previous study with chronic MDD found a higher prevalence (75.6%), suggesting that rates in chronic and/or recurrent MDD may be higher than in non-chronic/non-recurrent persons,(Negele et al., 2015) and our study seems to be consistent with these rates as we found a rate slightly higher than that of a recent meta-analysis (2017).(Nelson et al., 2017b) Our finding that emotional abuse and neglect were the most frequent types of CMT also agrees with several previous studies exploring prevalence in MDD.(Negele et al., 2015; Nelson et al., 2017b) In our sample of chronically and/or recurrently depressed individuals, three quarters of those with history of CMT reported experiencing multiple types which is in agreement with

Table 3
Effect size[a] of the associations between different types of childhood maltreatment (CMT) in demographics and clinical variables in individuals with major depressive disorder (MDD) (N = 663).

Variables	Sexual Abuse n = 145	Emotional Abuse N = 261	Physical Abuse n = 131	Neglect n = 240
Categorical Variables	Cohen's d	Cohen's d	Cohen's d	Cohen's d
Female gender	0.60**	0.02	0.08	0.02
Onset of MDD before age 18	0.51**	0.68***	0.39**	0.59**
Previous suicide attempts	0.34*	0.23*	0.36**	0.24*
Atypical features	0.13*	0.33*	0.18*	0.27*
Melancholic features	0.27*	0.15*	0.10*	0.06
Continuous Variables	Cohen's d	Cohen's d	Cohen's d	Cohen's d
MDD Characteristics				
Age at onset (MINI)	0.67***	0.72***	0.53**	0.59**
Number of previous MDD episodes (n = 507)	0.08	0.25*	0.15*	0.21*
Duration of current MDD episode	0.26*	0.28*	0.27*	0.17*
MDD Severity				
QIDS-SR	0.41**	0.47**	0.36**	0.44**
QIDS-C	0.37**	0.38**	0.32*	0.34*
IDS-C	0.46**	0.44**	0.40**	0.36**
HAM-D_{17}	0.24*	0.29*	0.36**	0.22*
Overall Impairment				
Quality of life (QOLI)	0.39**	0.47**	0.24*	0.44**
Work and social impairment (WSAS)	0.19*	0.37**	0.38**	0.44**
Number of psychiatric comorbidities	0.21*	0.38**	0.39**	0.36**

[a] Effect sizes (EF) compare participants who reported the type of CMT versus participants who did not report the type of CMT. EF: * = small ($0.10 \leq EF < 0.35$); ** = medium ($0.35 \leq EF < 0.65$); *** = large ($0.65 \leq EF$). Bold = medium or large effect size.

previous findings. For example, previous studies in community samples observed that with at least 50% of persons with CMT reported being exposed more than one kind of CMT.(Dong et al., 2004; Green et al., 2010) Negele et al. (2015) observed 55.1% of chronically depressed individuals had more than one type of CMT.(Negele et al., 2015) Therefore, the significant overlap between multiples types of CMT seems characteristic of many with chronic and/or recurrent MDD with a history of CMT. We also observed that physical abuse very rarely occurs alone (1.5% of the cases), and that it has a strong association particularly with emotional abuse (96% of the individuals with physical abuse also had emotional abuse).

Panic/phobia, cognitive and anhedonia were most strongly associated with CMT, consistent with previous clinical, neuroimaging and cognitive studies. With regards to anxiety-like symptoms (panic/phobia), our finding is consistent with the results of Klein et al. (2009) who observed an association between CMT,(Klein et al., 2009) particularly maternal overcontrol, and anxiety disorders. Another study found MDD with CMT showed greater amygdala activation in response sad faces relative to MDD without a history of CMT. (Grant et al., 2011) A recent 2-year longitudinal study with 110 depressed individuals found that reduced cortical surface area in the insula, a limbic structure associated with emotional awareness, mediated the relationship between CMT and future relapse in MDD.(Opel et al., 2019) With respect to anhedonia, a study with 183 medically healthy youths (61 with previous history of PTSD due to CMT and 122 controls without CMT) found that those who suffered CMT had volumetric reductions in posterior reward areas when compared to individuals without CMT. (De Bellis and Zisk, 2014a) From a cognitive-behavioral perspective, previous research found that people with CMT have more negative cognitive schemas related to perception of danger/vulnerability (which increases the likelihood of anxious-like and avoidant symptoms) and more negative cognitive schemas associated to worthlessness (which facilitates the development of anhedonic symptoms).(Lumley and Harkness, 2007) Taking these findings together, people with MDD and CMT seem to have a higher propensity for emotional (negative and positive valence symptoms) and cognitive complaints in MDD than people with MDD but no CMT. The finding regarding cognitive complaints is consistent with previous research by Vares et al. (2015). (Vares et al., 2015) In addition, history of CMT was associated with numerically higher rates of atypical features and melancholic features but only the former was statistically significant after controlling for multiple comparisons ($p < .001$ for atypical features; $p = .046$ for melancholic features). The greater prevalence of atypical MDD in individuals with CMT is consistent with previous work.(Klein et al., 2009; Levitan et al., 1998; Withers et al., 2013) It is not completely clear the reasons of this associations. It is possible chronic disruptive inflammatory response to threat moderates the relationship between CMT and atypical depression. (Danese et al., 2007; Lamers et al., 2013)

Individually, all types of CMT were related to a worse clinical presentation, but there were no compelling clinical differences among the distinct types of CMT. The significant overlap between these different types of CMT make it difficult to directly compare individual forms of CMT. Nonetheless, emotional abuse had the most robust association with earlier onset MDD, increased severity of MDD, and poorer quality of life. This is consistent with previous research that suggest that emotional (psychological) abuse and neglect have the strongest association with risk of MDD and worse clinical characteristics. (Hovens et al., 2015; Mandelli et al., 2015) Emotional abuse and neglect tend to be more chronic and more consistently effect development.(Spinazzola et al., 2014) Exposure to different types of CMT was associated with a worse clinical presentation. This observation reinforces the need for early intervention in cases of CMT in order to avoid the accumulation of distinct types of CMT. Acute interventions may improve the child's environment, avoid/reduce the development of excessively distorted cognitive schemas and facilitate access to care. This is especially salient when considering that 60% of the individuals with MDD and CMT had the onset of MDD before age 18. With regards to age of CMT exposure, individuals who have suffered CMT younger (latency phase) had no significant clinical differences when compared to individuals who suffered CMT in later (adolescence). Our finding is consistent with previous research by Gomez et al. (2017) who investigated 9272 adolescents and failed to observe differential associations between age of CMT and suicidality.(Gomez et al., 2017) On the other hand, previous studies showed that adverse life events in early life are more strongly associated with MDD and suicidal ideation than CMT in adolescence.(Dunn et al., 2013) The association between age of CMT and worse clinical characteristics in MDD remains unclear and there is a need for further studies investigating this relationship.

Why might CMT be associated with worse clinical presentation in chronic and/or recurrent depression? Several intertwined mechanistic processes might be involved. Early exposure to traumatic experiences could lead to epigenetic changes that promote long-lasting impairment in the hypothalamic-pituitary-adrenal (HPA) axis, expression of glucocorticoid receptors and levels of inflammatory markers. (Baumeister et al., 2016; De Bellis and Zisk, 2014b) Previous studies found abnormally elevated levels of cortisol(Douven et al., 2017; Heim et al., 2008) and increased concentrations of different inflammatory markers(Baumeister et al., 2016) in depressed adults with a history of CMT. Increased inflammation leads to several negative consequences, including decreased neurogenesis in the hippocampus, which is a well-established neurobiological change seen in MDD. (Baumeister et al., 2016) Chronic inflammation has been also associated with impairment in cognition and positive valence systems. (Medeiros et al., 2020b; Vares et al., 2016) Abnormalities in the HPA axis also increase the risk of anxiety symptoms/disorders, trauma-related disorders and general medical disorders leading to a complex

Table 4
Demographics and clinical variables in individuals with major depressive disorder (MDD), according to number of types of childhood maltreatment[a] (CMT) (N = 663).

Variables	Number of Childhood Maltreatment				Statistics	
	No CMT n = 332	One Type of CMT n = 85	Two Types of CMT n = 105	Three or Four Types of CMT n = 141	Statistical Significance	Effect Size[b]
DEMOGRAPHICS						
Categorical Variables	(%)	(%)	(%)	(%)	p^c	Cohen's d
Female gender	65%	74%	64%	75%	.072	0.23*
White race	64%	61%	66%	65%	.787	0.02
Hispanic ethnicity	15%	18%	14%	14%	.737	0.03
Continuous Variables	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p^d	Cohen's d
Age	44.2 (13.0)	41.0 (13.5)	42.2 (13.5)	40.8 (12.0)	.048	0.27*
Years of education	13.8 (2.8)	14.3 (3.0)	14.0 (3.0)	13.3 (3.4)	.142	0.17*
Body mass index	31.1 (8.4)	33.1 (10.4)	29.3 (8.0)	30.9 (9.2)	.176	0.02
CLINICAL VARIABLES						
Categorical Variables[d]	(%)	(%)	(%)	(%)	p^c	Cohen's d
MDD Characteristics						
Onset of MDD before age 18	29%	48%	60%	67%	< 0.0001	0.77***
Current suicidal ideation	52%	64%	67%	69%	.0006	0.35**
Previous suicidal attempts	5%	10%	9%	18%	< 0.0001	0.41**
Atypical features	13%	25%	23%	25%	.003	0.31*
Melancholic features	30%	37%	34%	41%	.043	0.22*
Psychiatric Comorbidities[e]						
Agoraphobia	6%	8%	16%	17%	.0003	0.34*
Alcohol abuse	9%	17%	10%	9%	.965	0.01
Bulimia	9%	14%	13%	15%	.104	0.17*
Generalized anxiety disorder	15%	17%	23%	30%	.0005	0.35**
Obsessive-compulsive disorder	10%	15%	12%	15%	.142	0.16*
Panic disorder	8%	6%	11%	16%	.007	0.26*
Post-traumatic stress disorder	9%	12%	11%	22%	.0003	0.38**
Social phobia	21%	33%	28%	36%	.004	0.31*
Continuous Variables	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p^d	Cohen's d
MDD Characteristics						
Age at onset (MINI)	28.8 (14.3)	21.7 (12.5)	20.0 (12.6)	17.2 (11.4)	.0003	0.90***
Number of previous MDD episodes (n = 507)	7.4 (13.8)	15.2 (25.7)	28.4 (116.5)	18.1 (29.2)	.004	0.32*
Duration of current MDD episode	47.8 (86.0)	74.3 (115.7)	68.4 (114.8)	82.7 (125.4)	.024	0.32*
MDD Severity						
QIDS-SR	14.5 (4.2)	16.0 (4.1)	16.0 (4.2)	17.1 (3.9)	< 0.0001	0.63**
QIDS-C	15.2 (3.4)	15.9 (3.6)	16.2 (3.5)	17.0 (3.1)	< 0.0001	0.54**
IDS-C	36.7 (8.9)	39.0 (9.4)	38.8 (8.9)	42.3 (8.7)	< 0.0001	0.63**
HAM-D_{17}	23.3 (4.7)	23.9 (4.6)	23.8 (5.0)	25.2 (4.8)	< 0.0008	0.40**
Overall Impairment						
Quality of life (QOLI)	24.4 (13.5)	18.1 (14.1)	19.3 (14.1)	16.1 (13.0)	< 0.0001	0.62**
Work and social impairment (WSAS)	25.3 (9.1)	27.2 (8.4)	27.9 (8.9)	29.9 (7.4)	< 0.0001	0.53**
Number of psychiatric comorbidities (PDSQ)	1.0 (1.5)	1.4 (1.5)	1.4 (1.6)	1.8 (1.8)	< 0.0001	0.50**
Number of medical comorbidities	1.9 (1.5)	1.9 (1.5)	1.9 (1.7)	2.1 (1.5)	.211	0.13*

[a] Fourtypes of CMT were assessed: sexual abuse, emotional abuse, physical abuse and neglect. [b] Effect size (EF) of difference between individuals without CMT and individuals in the group with 3 or 4 types of CMT. EF: * = small (0.10 ≤ EF < 0.35); ** = medium (0.35 ≤ EF < 0.65); *** = large (0.65 ≤ EF). [c] p value for Cochran-Armitage test. [d] p value for F test for linear trend contrast. [e] IQR = Interquartile Range. Categorical frequencies were assessed for trend with increasing numbers of CMT using Cochran-Armitage test while trend in mean levels of continuous variables were assessed using F test for a linear trend. Bold = high statistical significance (p < .001). IDS-C = the 30-item Inventory of Depressive Symptomatology - Clinician Version.

clinical presentation.(Briere et al., 2008; Danese et al., 2009; Medeiros et al., 2020a, 2020c) Collectively, these neurobiological changes might reduce responsiveness to medications and psychotherapy(Nanni et al., 2012). It is crucial for the clinician to have persistence, and serve as a non-threatening positive model for the maltreated individual.(Gabbard, 2017; McKay et al., 2019) In the long-term, these attitudes combined with pharmacotherapeutic and social interventions may reverse, attenuate, or compensate these trauma-related neurobiological changes and the consequent symptoms.

It is important to routinely assess for CMT in depressed individuals because a history of CMT has several implications in patient care. First, the report of one type of CMT may suggest other non-reported CMT. Second, a history of CMT indicates a higher risk of some symptoms (such as panic/phobia, cognitive complaints and positive valence symptoms) and comorbidities (particularly anxiety disorders and PTSD), that may benefit from additional more targeted interventions. (Bandelow et al., 2012; Medeiros et al., 2020b) Third, individuals with CMT showed poorer quality of life and greater work and social impairment, which suggests poorer social interactions/skills and lower resilience. These patients might benefit from non-pharmacological interventions such as psychotherapy, peer-support and social services. (Oral et al., 2016) Some useful techniques might be also briefly utilized in medication management appointments including problem solving strategies, cognitive reframing and other elements of trauma-focused psychotherapy.(Medeiros et al., 2019)

With respect to specific types of CMT, our data suggest that emotional abuse and neglect had a slightly stronger association with some important negative characteristics of adult MDD such as more frequent onset of MDD before age 18, higher number of previous depressive episodes and reduced quality of life. This is consistent with a previous meta-analysis by Nelson et al. (2017).(Nelson et al., 2017b) However, our results found that the link between particular clinical features of MDD and specific types of CMT is not compelling. Whether screening for or examining in depth the various types of CMT has clinical value remains to be determined. However, failing to identify CMT when present may overlook the need for additional targeted treatment.

Our data show that further research is needed to clarify clinical particularities of distinct types of CMT. Relevant challenges for routine

CMT evaluation include: 1) the short duration of the appointments and 2) doctors' concerns such as lack of training in asking about CMT and fear of inducing negative consequences in the patients.(Becker-Blease and Freyd, 2006) With respect to the time constraint, a systematic review of more than 28 million medical visits in 67 countries found that a primary care appointment lasts on average 5 min or less for half of the world population.(Irving et al., 2017) This is concerning because most patients with MDD are seen in primary care settings. (Unutzer and Park, 2012) Appointments with psychiatrists tend to be longer (average of 22 [SD = 12]) minutes in the United States. (Cruz et al., 2013) However, complaints of overwork, excessive patient load and burdensome paperwork requirements are common. (Kumar, 2007) In addition, previous work suggests that asking about CMT appears not to have harmful consequences.(Becker-Blease and Freyd, 2006) Therefore, the development and further validation of standardized, very brief questionnaires that assess CMT, such as the one used in this study, might facilitate the reliable, effective and time-efficient assessment of CMT in clinical practice.

4.1. Limitations

Our results should be interpreted in light of the study limitations. First, CMT was evaluated based on retrospective self-report. Previous research found some inconsistencies between prospective and retrospective assessments of CMT, and the latter may overestimate CMT. (Baldwin et al., 2019) In addition, memory is a very intricated cognitive process, and deficits encoding memory in early life, source-memory error, emotional valence associated with the CMT, and fear of the consequences of reporting a CMT are possible biases when assessing for CMT in depressed individuals.(Baldwin et al., 2019; Bennett, 2014) There are additional emotional and cognitive characteristics of depressed individuals that may make the assessment of CMT even more challenging such as significant emotional dysregulation, depressive ruminations and cognitive impairment secondary to MDD. (Kircanski et al., 2012) Examining age when CMT occurred seems to be particularly vulnerable to biases in the setting of long intervals between the CMT and the time of the interview.(Sedgwick, 2012)

Second, there are potential some language and terminology limitations in our survey of CMT. The questions assessing CMT asked if the participants *believed* they were abused, and allowed participants to define abuse. Despite this, the prevalence of CMT in our sample (approximately 50%) was very similar to previous studies,(Negele et al., 2015; Nelson et al., 2017a) including a comprehensive meta-analysis of 184 that observed a CMT prevalence of 46%.(Nelson et al., 2017a) We also did not assess either the duration or the intensity of CMT which might impact the relationship between CMT and MDD clinical presentation.(Heim and Nemeroff, 2001) Third, personality disorders, which might possibly moderate some of the findings, were not examined in the CO-MED study.

Finally, the questionnaire that investigated CMT was not previously used and it needs further assessment of its validity (does the test reflect CMT) and reliability. Whether these results in treatment-seeking outpatients with chronic or recurrent MDD generalize to other samples is unknown. We may have had too few participants to detect differences between people with varying types of CMT, and we did not investigate other childhood experiences that some consider CMT (e.g. death of friend/family, divorce of parents or violence towards another family member).

5. Conclusions

Half of treatment-seeking outpatients with chronic and/or recurrent depression, report CMT (and typically multiple types) which is associated with a worse clinical presentation in MDD. All types of CMT were associated with worse clinical presentation, and those with more than one type showed greater impairment. The recognition of CMT in practice might help treatment selection and management.

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Contributors

Conceptualization: GCM, AM, AJR, MHT; Data curation: AM, MHT; Formal analysis: AM; Funding acquisition: MHT, AJR; Investigation: AJR, MHT; Methodology: GCM, AM, AJR, MHT; Project administration: AJR, MHT; Resources: AJR, MHT; Software: AM; Supervision: MHT; Validation: AM; Visualization: GCM, WLP, AM, AHC, AJR, MHT; Writing – original draft: GCM, WLP, AM, JLF, AJR, MHT. Writing – reviewing and editing: GCM, WLP, AM, SSP, AHC, JLF, BLM, AJR, MKJ, MHT.

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Declaration of Competing Interest

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Supplementary materials

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