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Late-Life Depression, Hippocampal Volumes, and Hypothalamic-Pituitary-Adrenal Axis Regulation: A Systematic Review and Meta-analysis

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ABSTRACT

BACKGROUND: We systematically reviewed and meta-analyzed the association of late-life depression (LLD) with hippocampal volume (HCV) and total brain volume (TBV), and of cortisol levels with HCV, including subgroup analyses of depression characteristics and methodological aspects.

METHODS: We searched PubMed and Embase for original studies that examined the cross-sectional relationship between LLD and HCV or TBV, and 46 studies fulfilled the inclusion criteria. Standardized mean differences (Hedges' *g*) between LLD and control subjects were calculated from crude or adjusted brain volumes using random effects. Standardized Fisher transformations of the correlations between cortisol levels and HCVs were calculated using random effects.

RESULTS: We included 2702 LLD patients and 11,165 control subjects from 35 studies examining HCV. Relative to control subjects, patients had significantly smaller HCVs (standardized mean difference = –0.32 [95% confidence interval, –0.44 to –0.19]). Subgroup analyses showed that late-onset depression was more strongly associated with HCV than early-onset depression. In addition, effect sizes were larger for case-control studies, studies with lower quality, and studies with small sample size, and were almost absent in cohort studies and studies with larger sample sizes. For TBV, 2523 patients and 7880 control subjects from 31 studies were included. The standardized mean difference in TBV between LLD and control subjects was –0.10 (95% confidence interval, –0.16 to –0.04). Of the 12 studies included, higher levels of cortisol were associated with smaller HCV (correlation = –0.11 [95% confidence interval, –0.18 to –0.04]).

CONCLUSIONS: While an overall measure of LLD may be associated with smaller HCVs, differentiating clinical aspects of LLD and examining methodological issues show that this relationship is not straightforward.

Keywords: Aging, Cortisol, Hippocampus, Late-life depression, Meta-analysis, MRI

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Major depressive disorder (MDD) is the most common psychiatric disorder, with a lifetime prevalence of about 15% to 20% worldwide (1,2). MDD is a severely disabling disorder, but treatment success is relatively low—only one in three patients may achieve remission after treatment (3). Consequently, it is important to understand the underlying pathophysiology of MDD. Many studies observed morphological brain changes related to MDD showing that particularly hippocampal, medial prefrontal cortex, and basal ganglia areas are affected by MDD in adult populations (4–8).

At older age, MDD is relatively rare, but clinically relevant elevated depressive symptoms frequently occur (9) and often persist over years (10). Several studies have shown that depression later in life is associated with brain volume reductions (11,12) and an increased risk of dementia (13,14). One often-proposed explanation for this relationship is the neurotoxic effect of dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (15). Functional changes of the HPA axis have consistently been reported in MDD (16), and these may be even more apparent later in life (17), because with increasing age the HPA axis is less adaptive in its responses, leading to a flattened diurnal rhythm (18). Moreover, several studies, predominantly in rodents, found that stress-related increase of glucocorticoids was associated with morphological brain changes, particularly hippocampal volume (HCV) loss (19,20). However, few studies in older human populations have examined the relationship between late-life depression (LLD), HPA axis activity, brain volume loss, and the risk of dementia. In addition, because of the lack of longitudinal studies, the direction of association is unclear, and we do not know whether depression is a contributor to this increased risk or a consequence of brain volume changes and incipient dementia. In addition, LLD is defined as depression occurring later in life (>50 years of age), regardless whether it is or is not the first episode of depression. Thus, LLD includes first-onset

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depression (i.e., late-onset depression [LOD]) and early-onset depression (EOD). EOD is defined as a first onset earlier in life and may be recurrent or chronic until later life; it may also be a single episode earlier in life until it recurs later in life. As such, it encompasses different categories with different etiologies. It is therefore possible that the morphological brain changes are different for EOD and LOD. It has also been suggested that EOD is more strongly associated with HCV loss than LOD (12). A possible explanation for this finding is that because of the earlier onset and often recurrent nature of MDD, the hippocampus has had more exposure to the potentially detrimental effects of HPA axis dysregulation associated with (chronic) MDD (21). A recent meta-analysis on morphological brain changes in LLD showed that the most consistent evidence for brain volume reductions were found for the hippocampus but not for any of the other brain areas (22). In this meta-analysis, no distinction was made between EOD and LOD. Thus, an updated meta-analysis is needed that elucidates the influence of age of depression onset.

Another aspect that needs clarification is to what extent depression characteristics, such as assessment of LLD (clinical diagnosis vs. depressive symptom questionnaire), and recurrence and duration of depression are differentially related to HCV. Also, methodological issues such as design and sample size need to be examined. We will also examine lateralization effects in the hippocampus; several studies have found that MDD differentially affects the left and right hippocampus (7,8).

In addition to examining the relation between LLD and brain volumes in greater detail, we will also review and meta-analyze one of the most often proposed explanations for this relationship, which is dysregulation of the HPA axis (23).

Our aim was to systematically review and meta-analyze 1) the relation between LLD and hippocampal and total brain volumes (TBVs), including subgroup analyses of early or late onset, depression assessment, design, and sample size; and 2) the relation between HPA axis dysregulation and HCVs at older age.

METHODS AND MATERIALS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (24).

Literature Search and Study Selection

We searched PubMed and Embase for studies published before June 15, 2015 (for LLD with HCV or TBV) or August 28, 2015 (for HPA axis with HCV) using the search terms shown in Supplemental Table S1. We used broad eligibility criteria for inclusion to be able to examine clinical and methodological moderators (Supplemental Table S2). We performed quality assessment of studies with the Newcastle-Ottawa Quality Assessment Scale for case-control and cohort studies (www.ohri.ca/programs/clinical_epidemiology/oxford.asp) and performed stratified analyses on lower and higher quality of studies. Inclusion and exclusion criteria for studies on HPA axis and HCV are described in Supplemental Table S2. Studies were selected first by screening title and abstract. If a study appeared relevant, the full text was reviewed to identify whether it fulfilled the inclusion and exclusion criteria. Both authors independently performed study selection, with discrepancies resolved by consensus.

Statistical Analysis

To investigate the relationships of LLD with HCV and TBV, we extracted from all studies the fully adjusted means, or crude means if adjusted were not reported, for participants with and without LLD. For nine articles, authors were contacted (11,12,25–31). Using the "meta" package (version 4.3-0) in R (version 3.2.1; www.r-project.org/), we modeled the standardized mean differences (SMDs, Hedges' g) between LLD and control subjects with the restricted maximum-likelihood estimator for tau squared, using random effects in the function "metacont." Heterogeneity was assessed with I^2. Metaregression and subgroup analyses were run for the following moderators: mean age, percentage female, sample size (continuous and $n < 100$ vs. $n \geq 100$ participants), study design (case-control vs. cohort study), setting (community, in- and outpatients combined, and outpatients only), quality of studies (<6 vs. ≥ 6 stars), year of publication, depression assessment (clinical diagnosis vs. cut-off of depressive symptoms questionnaire), age of onset (EOD vs. LOD), duration of LLD (calculated as mean age at time of magnetic resonance imaging [MRI] minus mean age at first onset), current or remitted LLD, hemisphere (left vs. right HCV), manual versus automated segmentation of the hippocampus, adjustment for cardiovascular risk factors, and exclusion of dementia.

To investigate the relation between cortisol levels and HCVs in older age, we extracted from all studies the fully adjusted or crude correlations if adjusted correlations were not reported. We modeled the standardized Fisher transformations of the correlations between HCVs and cortisol levels, using random effects in the "metacor" function. First, the overall correlation was estimated regardless of timing of cortisol measure, and then subgroup analysis was run to investigate the effect of time of cortisol sampling (morning, evening, diurnal mean, and morning cortisol after dexamethasone suppression test).

To examine publication bias, we computed funnel plots and computed Egger's t statistics.

RESULTS

LLD and Brain Volumes

The initial search identified 994 records in PubMed and 1345 records in Embase. After exclusion of duplicates, 1807 records were screened on title and abstract, 255 of which were read in full text, and 44 were included in the meta-analysis. Two articles were additionally included from reference lists (snowballing; Supplemental Figure S1) (11,12,25–68).

Supplemental Table S3 presents the study characteristics. Table 1 presents the main findings of the 46 included studies. LLD was assessed with clinical diagnostic criteria in 33 studies (72%). A case-control design was used in 35 studies (76%). In 22 studies (48%), the total sample size was ≥100 participants. In 36 studies (78%), current LLD was reported; in 8 studies, lifetime LLD, including current LLD and remitted LLD, was reported; and in 2 studies, remitted LLD was reported. EOD was distinguished in 15 studies (33%) and LOD also in 15 studies. Medication use was reported in 26 studies (54%), of

Table 1. Main Findings of 46 Studies on Late-Life Depression and Structural Brain Correlates

	MRI Characteristics				
Author, Year	T	ROI	Segmentation Method	Analysis	Main Findings
Almeida *et al.*, 2003 (32)	1.0	TBV	Manual	TBV, age, and sex	NS
Andreescu *et al.*, 2008 (33)	1.5	TBV, HC	Automated	Primary visual cortex volume	TBV: NS HC: LLD < CON
Ashtari *et al.*, 1999 (34)	1.0	TBV, HC	Semiautomated	Age, sex, and height	NS
Ballmaier *et al.*, 2004 (35)	1.5	TBV	Automated	NR	NS
Ballmaier *et al.*, 2008 (36)	1.5	TBV, HC	Automated	TBV, age, and sex	TBV: NS HC: LLD < CON
Benjamin *et al.*, 2010 (37)	1.5	TBV, HC	Semiautomated	NR	NS
Brown *et al.*, 2014 (25)	1.5	HC	Automated	TBV, age, sex, education, race/ethnicity, psychotropic medications, and alcohol use	LLD < CON
Burke *et al.*, 2011 (38)	1.5	TBV	Automated	TBV, age, and sex	NS
Chang *et al.*, 2011 (39)	1.5	TBV	Automated	Age and sex	NS
Colloby *et al.*, 2011 (40)	3.0	TBV, HC	Automated	Intracranial volume	NS
Delaloye *et al.*, 2010 (41)	3.0	HC	Manual	Intracranial volume and age	NS
Elbejjani *et al.*, 2015 (26)	1.5	HC	Automated	Intracranial volume, age, and sex	NS
Elcombe *et al.*, 2015 (27)	3.0	TBV, HC	Semiautomated	Intracranial volume, age, and sex	NS
Enache *et al.*, 2014 (42)	1.5	HC	Manual	Age, sex, education, and MMSE	LLD < CON
Ezzati *et al.*, 2013 (43)	NR	HC	Manual	Age, sex, and education	LLD < CON
Geerlings *et al.*, 2008 (11)	1.5	HC	Manual	Intracranial volume, age, sex, education, MMSE, and subjective memory complaints	NS
Geerlings *et al.*, 2012 (28)	1.5	TBV, HC	Automated	Intracranial volume, age, sex, education, MMSE, subjective memory complaints, smoking, alcohol, BMI, blood pressure, diabetes, history of stroke, WML volume, and infarcts on MRI	LLD < CON
Geerlings *et al.*, 2013 (29)	1.5	TBV, HC	Automated	Intracranial volume, age, sex, education, ethnicity, cardiovascular disease history, WML volume, and presence of infarct on MRI	LLD < CON
Gerritsen *et al.*, 2011 (12)	1.5	TBV, HC	TBV: automated HC: manual	Intracranial volume, age, sex, education, BMI, diabetes, blood pressure, smoking, alcohol, antidepressants, and WML volumes	TBV: NS HC: EOD < CON LOD: NS
Goveas *et al.*, 2011 (44)	NR	TBV, HC	Automated	Intracranial volume, age, education, ethnicity, Women's Health Initiative treatment assignment, clinic, time between enrollment and MRI, 3MS score, BMI, smoking, previous use of hormone therapy, antidepressants, CVD, diabetes, and hypertension	NS
Hickie *et al.*, 2005 (45)	1.5	TBV, HC	Manual	TBV and age	TBV: LLD < CON HC: LLD < CON
Hou *et al.*, 2012 (46)	1.5	HC	Manual	Intracranial volume	LLD < CON
Janssen *et al.*, 2004 (47)	1.5	TBV, HC	TBV: automated HC: manual	TBV, age, handedness, and education (matching)	TBV: NS HC: LLD < CON
Janssen *et al.*, 2007 (48)	1.5	TBV, HC	TBV: automated HC: manual	TBV: intracranial volume HC: TBV, age, and MMSE	TBV: LOD < CON HC: EOD < CON
Jayaweera *et al.*, 2015 (49)	3.0	HC	Semiautomated	NR	NS
Köhler *et al.*, 2010 (50)	1.0	TBV, HC	TBV: semiautomated HC: manual	TBV	NS
Kumar *et al.*, 2000 (51)	1.5	TBV	Semiautomated	Intracranial volume, age, and sex	NS
Lee *et al.*, 2014 (52)	1.5	HC	Automated	Age, sex, education, MMSE, and intracranial volume	NS
Lim *et al.*, 2012 (54)	3.0	HC	Automated	Intracranial volume, age, sex, and education	Right HC: LLD < CON Left HC: NS
Lim *et al.*, 2012 (53)	3.0	HC	Automated	Intracranial volume, age, sex, and education	LLD < CON
Lloyd *et al.*, 2004 (55)	1.5	TBV, HC	Automated	Intracranial volume	TBV: NS HC: LLD < CON
Naismith *et al.*, 2002 (56)	1.5	TBV	Manual	NR	LLD < CON
O'Brien *et al.*, 2004 (57)	1.0	TBV, HC	TBV: automated HC: manual	HC: TBV	TBV: NS Right HC: LLD < CON Left HC: NS

Table 1. Continued

Author, Year	MRI Characteristics: T	MRI Characteristics: ROI	Segmentation Method	Analysis	Main Findings
Oudega *et al.*, 2014 (58)	1.0	TBV	Automated	NR	NS
Pantel *et al.*, 1997 (59)	1.5	TBV	Automated	Intracranial volume	LLD < CON
Ritchie *et al.*, 2012 (60)	1.5	HC	Manual	TBV	NS
Sawyer *et al.*, 2012 (61)	1.5	TBV, HC	Semiautomated	NR	NS
Sexton *et al.*, 2012 (62)	3.0	TBV, HC	Automated	TBV: age and sex HC: age, sex, and TBV	TBV: LLD < CON HC: NS
Sheline *et al.*, 2012 (63)	1.5	HC	Automated	Age, education, and Framingham vascular risk score	LLD < CON
Soriano-Mas *et al.*, 2011 (64)	1.5	TBV	Automated	NR	NS
Taylor *et al.*, 2005 (65)	1.5	HC	Semiautomated	TBV, age, and sex	NS
Taylor *et al.*, 2007 (66)	1.5	TBV	Semiautomated	NR	NS
van Uden *et al.*, 2011 (30)	1.5	TBV	Automated	Intracranial volume, age, sex, WML, and lacunar infarcts	NS
Weber *et al.*, 2010 (67)	3.0	TBV, HC	Automated	Intracranial volume	NS
Wisse *et al.*, 2015 (31)	7.0	HC	Manual	Intracranial volume, age, sex, and education	NS
Zhao *et al.*, 2008 (68)	3.0	TBV, HC	TBV: semiautomated HC: manual	TBV, age, and sex	LLD < CON

3MS, Modified Mini-Mental State test; BMI, body mass index; CON, controls/reference group; CVD, cardiovascular disease; EOD, early-onset depression; HC, hippocampus; LLD, late-life depression; LOD, late-onset depression; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NR, not reported; NS, not significant; ROI, region of interest; T, tesla; TBV, total brain volume; WML, white matter lesions.

which 11 (44%) reported that ≥50% of the patients were taking ≥1 medications at the time of MRI. MRI field strength ranged from 1.0 to 7.0 T, with the majority using 1.5 or 3 T. In 20 studies, HCV and TBV were reported, in 15 studies HCVs only, and in 11 studies TBV only. Of the 31 studies reporting TBV, 28 (90%) used (semi)automated techniques to segment tissue volume; of the 35 studies reporting HCVs, 21 (60%) used (semi) automated techniques.

Meta-analysis LLD with HCV. For HCV in total, 2702 patients and 11,165 control subjects were included in the meta-analysis. In all studies combined, lifetime LLD was associated with significantly smaller HCV ($Z = -4.94$, $p < .0001$) (Figure 1). The random effects model showed a SMD in total HCV between LLD and control subjects of –0.32 (95% confidence interval [CI], –0.44 to –0.19). Heterogeneity between studies was considerable, with I^2 of 70.6% ($p < .0001$).

Quality assessment is shown in Supplemental Table S4. None of the studies received the maximum number of nine stars, and the minimum awarded was three stars. Twelve studies received more than six stars, 21 studies received six stars, and 13 studies received seven or eight stars. Most of the variance in stars given was for the selection criterion.

Supplemental Table S5 shows the results of the moderator analyses for the number of studies that had data or reported the respective moderator. LOD versus never depressed was associated with a smaller HCV than EOD versus never depressed (Figure 2). In addition, studies using a diagnosis of MDD reported a larger effect size than studies using a cut-off of depressive symptoms (Supplemental Figure S2), as did case-control studies compared to cohort studies (Supplemental Figure S3), and settings where studies using in- and outpatients had larger effect estimates than community-based studies. Notably, smaller studies (total sample <100) had a much larger effect size than larger studies ($n \geq 100$), and the R^2 for sample size was considerable, with 89% (Supplemental Figure S4). We found no evidence for a lateralization effect of MDD on HCV (Supplemental Figure S5). Subgroup analyses on adjustment for cardiovascular risk factors or exclusion of dementia patients did not reveal differences in effect size, nor did mean age and percentage female.

When we stratified on quality assessment, we found that the studies with lower quality had stronger effect size than studies with higher quality (Supplemental Figure S6). However, when we performed multivariable metaregression, only sample size remained significant (Supplemental Table S6).

Meta-analysis LLD With TBV. For TBV in total, 2523 patients with LLD and 7880 control subjects from 31 studies were included. Lifetime LLD compared to control subjects was associated with significantly smaller TBV ($Z = -3.40$, $p = .0007$) (Supplemental Figure S7). The random effects model showed a significant SMD in TBV between LLD and control subjects of –0.10 (95% CI, –0.16 to –0.04). The I statistic for heterogeneity was not significant ($I^2 = 11.2\%$; $p = .29$).

The SMD for EOD versus never depressed was –0.18 (95% CI, –0.34 to –0.01) and for LOD was –0.04 (95% CI, –0.26 to 0.17). This difference was not significant ($\chi^2_1 = 0.92$, $p = .34$). Other moderators were also not significantly different (Supplemental Table S7).

Publication Bias. The Egger's t statistic for asymmetry in the funnel plot was significant for studies reporting on HCV (B for bias = –2.71; $t_{33} = -5.85$, $p < .0001$) (Supplemental Figure S8), as well as for TBV (B for bias = –1.63; $t_{29} = -2.75$, $p = .01$) (Supplemental Figure S9).

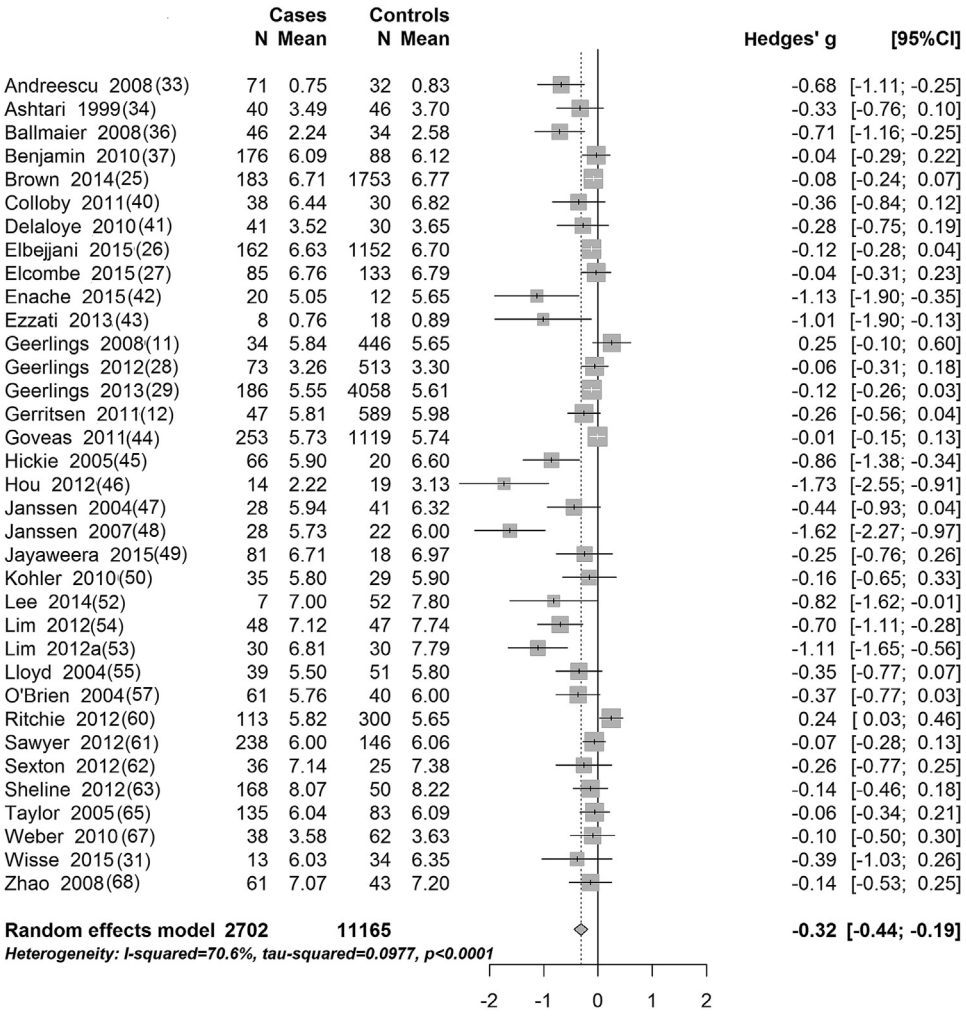

Figure 1. Standardized mean differences (Hedges' *g*) in hippocampal volume for patients with lifetime late-life depression (including current and remitted) compared with control subjects (older persons without a history of depression). CI, confidence interval.

Cortisol and HCV

The initial search identified 491 records, of which 404 were screened on title and abstract after duplicate removal, and 24 were read in full text. Sixteen papers were included in the qualitative analysis (57,69–83) and 12 in the meta-analysis (57,69,72–77,79–83) (Supplemental Figure S10).

Supplemental Table S8 presents the study characteristics. Table 2 presents the main findings of the 16 studies. The wide variation in study population, number of participants included, type and setting of measurement of cortisol, and mean level of cortisol are notable. Fifteen (94%) studies measured basal cortisol levels, and five (31%) studies measured HPA axis feedback inhibition using a dexamethasone suppression test. MRI field strength ranged from 0.35 to 3.0 T, and 11 studies (69%) used manual segmentation of HCV.

Meta-analysis Cortisol Levels and HCV. All studies taken together, higher levels of cortisol, regardless of timing of cortisol, were associated with smaller HCV (correlation = –0.11 [95% CI, –0.18 to –0.04]; $p < .01$). The I statistic for heterogeneity was significant ($I^2 = 69.6$, $p < .001$). Subgroup analysis showed that higher awakening cortisol levels after dexamethasone and higher basal evening cortisol levels were significantly associated with smaller HCV (cortisol after dexamethasone suppression test: correlation = –0.12 [95% CI, –0.20 to –0.05], $Z = –3.30$, $p < .01$; evening cortisol: correlation = –0.11 [95% CI, –0.17 to –0.04], $Z = –3.32$, $p < .01$). The other time measures showed similar correlations but did not reach statistical significance (12- or 24-hour cortisol: correlation = –0.18 [95% CI, –0.54 to 0.22], $Z = –0.94$, $p = .17$; morning cortisol: correlation = –0.11 [95% CI, –0.25 to 0.02], $Z = –1.60$, $p = .06$) (Figure 3).

There was no indication of publication bias (B for bias = –0.85; $t_{10} = –0.31$, $p = .76$).

DISCUSSION

This meta-analysis showed that lifetime LLD was significantly associated with smaller HCVs. Lifetime LLD was also significantly associated with smaller TBV, but the effect size was

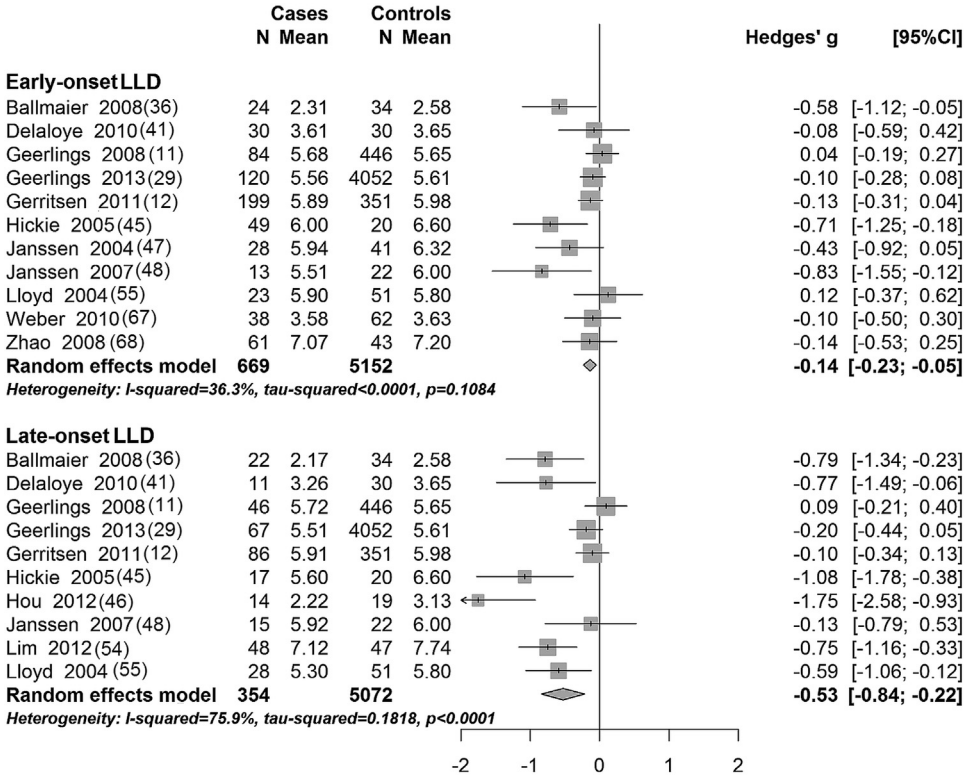

Figure 2. Standardized mean differences (Hedges' *g*) in hippocampal volume for patients with an early onset of depression (i.e., <50–60 years of age) vs. those never depressed, and for patients with a late onset of depression (≥50–60 years of age) vs. those never depressed. CI, confidence interval; LLD, late-life depression.

much smaller. Higher levels of cortisol had a weak relationship with HCV.

A preceding meta-analysis reported a similar effect size for HCV (–0.32) (22). Because we performed the literature search 5 years later and the majority of studies were published in or after 2010, we included 34 additional studies, enabling us to perform several subgroup analyses that revealed a number of things. First, LOD was more strongly associated with HCV than EOD. Second, studies that used a clinical diagnosis of depression found stronger associations than studies that used symptom questionnaires. Third, studies that used a manual segmentation method for HCV found a larger effect size than studies that used an automated segmentation method. Fourth, effect estimates were larger for case-control studies, studies with small sample sizes, studies with in- and outpatients, and studies with lower quality. Finally, although often suggested, no evidence of lateralization effects was observed, which is in line with findings from a recent meta-analysis that also included younger populations (5).

The finding that LOD was more strongly associated with HCV is contrary to findings from a recent meta-analysis (4) where early- but not late-onset MDD was associated with smaller HCVs. It should be noted that in the Enhancing Neuroimaging Genetics through Meta-analysis study, late onset was defined as >21 years of age and the mean age of the majority of studies included was <50 years. Because we included studies with a mean age of ≥55 years, the relationship between onset of depression and HCV could be different in early, middle, and late adulthood.

It has often been hypothesized in the epidemiologic literature that the increased risk of dementia associated with LLD is explained by the neurotoxic effects of high levels of cortisol on the hippocampus associated with repeated depressive episodes (15). This hypothesis predicts that in particular, older persons with a history of depressive episodes have an increased risk for dementia. Because most studies do not have detailed information on depression history, the distinction is often made between EOD and LOD, because LOD by definition is without a history earlier in life and EOD is likely to be followed by repeated episodes, given that a history of depression is a strong risk factor for new depressive episodes (84). Thus, EOD would then be expected to have a stronger relationship with reduction in HCV than LOD. However, we found the opposite. One interpretation is that LOD is a consequence or concurrent phenomenon of HCV reduction, perhaps as an early symptom of dementia. As such, it could even be that prodromal dementia leading to decreased HCV can result in increased levels of cortisol because of less negative feedback on the HPA axis. Indeed, higher levels of cortisol are common both in depression and dementia (85). We were not able to examine this because of the cross-sectional design, although the majority of studies—for those who reported this—excluded participants with dementia and cognitive impairment, and subgroup analysis did not reveal different effect estimates. Also, in later life, relatively few persons with depression have a first onset (29), and the majority of studies examine current LLD without discerning LOD from EOD.

Table 2. Main Findings of Studies on Hypothalamic-Pituitary-Adrenal Axis and Hippocampal Volume at Older Age

Author, Year	Field Strength (T)	Segmentation Tool	Adjustments	Main Finding Cortisol-Hippocampus
Bruehl *et al.*, 2009 (69)	1.5	Manual	Age, sex, diabetes diagnosis, hemoglobin A1c, and intracranial volume	Not significant
Cox *et al.*, 2015 (70)	1.5	Semiautomated	NR	Not significant
Ferrari *et al.*, 2000 (71)	0.35	Manual	NR	Impairment in nocturnal increase = smaller HC
Geerlings *et al.*, 2015 (72)	1.5	Automated	Evening cortisol: age, sex, education, smoking, steroid use, cardiovascular risk factors, intracranial volume, white matter lesions, and infarcts on MRI Morning cortisol: age, sex, education, smoking, steroid use, cardiovascular risk factors, intracranial volume, white matter lesions, infarcts on MRI, being currently employed, and sleeping problems	Higher evening cortisol level = smaller HC; morning cortisol: not significant
Gold *et al.*, 2005 (73)	1.5	Manual	Age, sex, and body mass index	Not significant
Knoops *et al.*, 2010 (74)	1.5	Manual	Age, sex, total brain volume, smoking, alcohol, body mass index, diabetes, systolic and diastolic blood pressure, hyperlipidemia, and disease history	High evening cortisol level = smaller HC; waking after DEX = smaller HC; and morning cortisol levels: not significant
Kremen *et al.*, 2010 (75)	1.5	Automated	Age, cognition, hypertension, cardiovascular disease, depression, diabetes, alcohol and smoking habits, batch, and site	Not significant
Lupien *et al.*, 1998 (76)	1.5	Manual	Head size	Increasing/high cortisol level = smaller HC
MacLullich *et al.*, 2005 (77)	1.9	Manual	Intracranial area	Not significant
Magri *et al.*, 2000 (78)	0.35	Manual	Age and intracranial volume	Only reported for dementia cases and controls together
O'Brien *et al.*, 2004 (57)	1.0	Manual	Age and total brain volume	Within MDD: not significant
O'Hara *et al.*, 2007 (79)	1.5	Semiautomated	Age and intracranial volume	Higher waking cortisol = smaller HC
Sindi *et al.*, 2014 (80)	1.5	Manual	Intracranial volume, total brain volume, age, and education	Not significant
Sudheimer *et al.*, 2014 (81)	1.5	Semiautomated	Age and sex	Higher cortisol level = smaller HC
Wolf *et al.*, 2002 (82)	1.5	Manual	Head size and age	Higher free 24-hour urinary cortisol level = smaller HC; morning blood cortisol level: not significant
Yehuda *et al.*, 2007 (83)	3.0	Manual	Total brain volume and age	Not significant

DEX, dexamethasone; HC, hippocampus; MDD, major depressive disorder; MRI, magnetic resonance imaging; NR, not reported; T, tesla.

Adding to this complexity, varying definitions of LLD are used in the literature, including whether a DSM diagnosis or a high score on a questionnaire is required. Second, some people may have had one depressive episode early in life and then only one episode at the time of MRI, and some people may have had more than one episode but only later in life. Third, not all studies reported the mean age at onset. For those that did, the mean age at onset ranged from 33 to 74 years, and the cut-off used for EOD versus LOD ranged from 45 to 60 years, a time window in which changes in the brain occur that may lead to clinical dementia 15 to 20 years later. Fourth, LOD and EOD have different etiologies, but in later life the distribution of risk factors in persons with EOD may have changed because of selective survival, and LOD and EOD become either more similar or more different in risk factor profile, leading to differential or unexpected associations with HCV. As such, no firm conclusions can be drawn from this meta-analysis because older persons with EOD may be a highly selective and potentially more resilient group of patients. Finally, a substantial portion of the studies did not adjust for cardiovascular risk factors or white matter hyperintensities (WMHs). Recurrent EOD has been found to increase vascular dementia, while LOD increased Alzheimer's disease risk (86), but LOD has also been associated with more WMHs compared to EOD (87). These findings seem contradictory, but it is more likely that different subgroups exist. For instance, in some older persons with recurrent EOD, cardiovascular risk may have accumulated into WMHs, while in others WMH, alone or in combination with hippocampal atrophy, may lead to LOD. In others, LOD may result from a psychological reaction to cognitive decline, or from psychosocial stress unrelated to brain changes. Obviously, to increase our understanding of the relationship between LLD and brain changes we need to better characterize subgroups of LLD and investigate the neurotoxicity and vascular hypothesis in conjunction.

We observed a stronger relationship with HCV for MDD diagnosis than for depressive symptoms. One explanation for this finding is that a clinical diagnosis better reflects clinically significant depression than a cut-off score on a depressive symptoms scale; also, a stronger contrast exists between MDD cases and control subjects. However, it is also possible

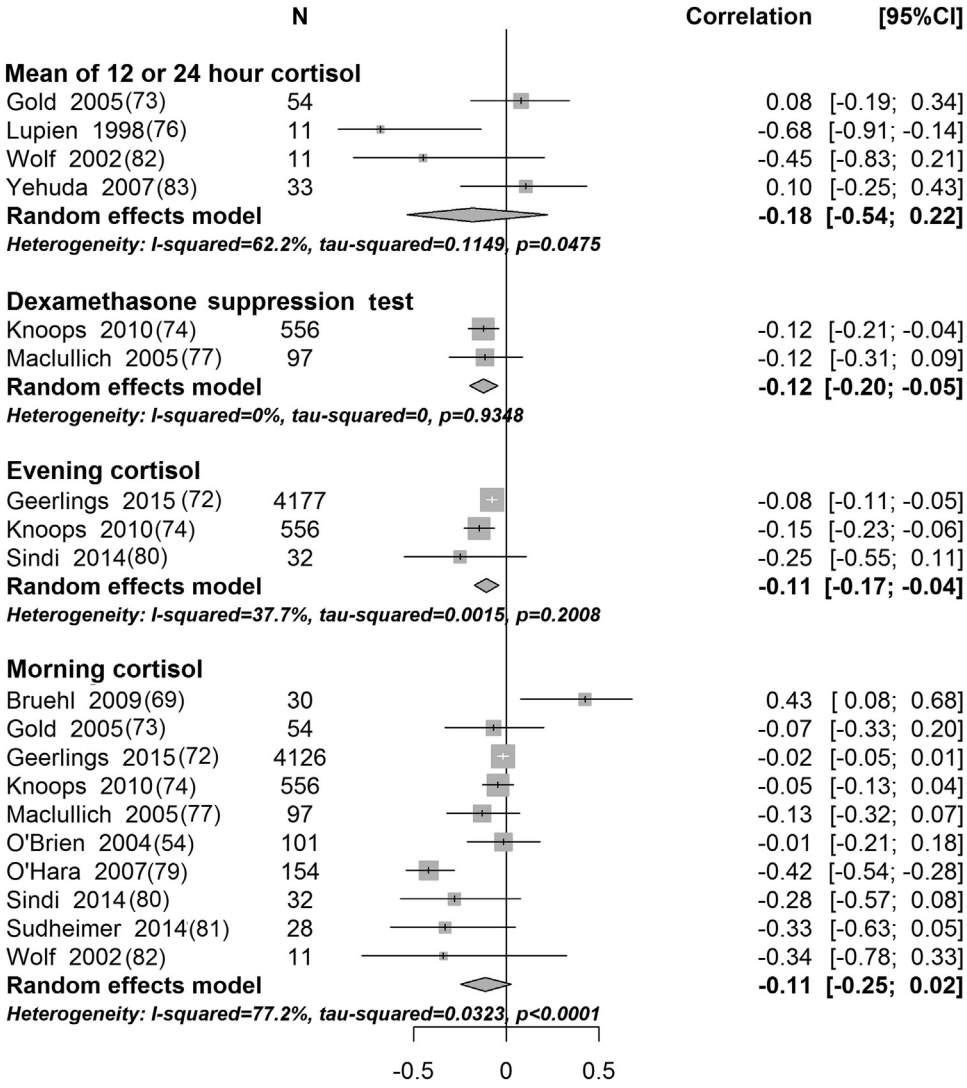

Figure 3. Standardized Fisher transformation of the correlations between cortisol levels and hippocampal volume, according to timing of cortisol. CI, confidence interval.

that the effect size of MDD diagnosis is overestimated because we also observed larger effect sizes in case-control studies. Case-control studies are highly prone to selection bias and are more likely include more severe cases of depression and have a hospital-based setting. With respect to duration of depression—for those studies from which we could calculate it (n = 20)—there was no effect of duration. The majority of studies compared currently depressed patients to control subjects, whereas some others included also remitted depression as cases. Our findings suggest that particularly a current episode of LLD is related to significantly smaller HCV, but this could also be because that this was the largest group.

A notable finding was that there was no relationship between LLD and HCV in studies that had a total sample size of ≥100 and that the high heterogeneity was largely accounted for by small sample size. Apart from this, publication bias appeared evident. In general, the factors that moderated the association tend to cluster together, i.e. case-control design, in- and outpatients, clinical diagnosis, manual segmentation of HCV, smaller sample size, and studies with lower quality. In the multivariable metaregression, sample size remained the only significant factor, but because of clustering it is difficult to disentangle them. At any rate, these findings cast doubt on the validity of the strongly held belief that LLD is associated with HCV reduction. Moreover, because we found many subgroup differences, they also stress the importance of differentiating the heterogeneous aspects of LLD in future studies.

This meta-analysis shows that the association of LLD with TBV is weak. Although publication biased seemed evident, there was little heterogeneity between studies and no subgroup differences were observed, suggesting that TBV has a general, although weak, association with LLD.

Few studies examined the relation between cortisol and HCV. Most studies measured cortisol levels in saliva, while some used peripheral blood or urine samples. Because there was some overlap between timing and sample type, it was not

possible to investigate whether sample type had impact on results, e.g. urine samples were usually overnight averages, whereas peripheral blood was usually taken sometime in the morning.

A recent review (88) suggested that particularly the mean of multiple samples collected during the day is a strong determinant of HCV, but this was not supported by our meta-analysis. Possible explanations for these different findings are that we focused on older populations, that we conducted an actual meta-analysis, and that we used a different definition of mean of diurnal cortisol. While Frodl *et al.* (88) grouped all studies that measured more than one sample during 1 day, we looked more specifically at the timing of sampling, because it is known that cortisol follows a specific diurnal rhythm. Despite the large heterogeneity in timing of sampling, setting (home vs. laboratory), mean level of cortisol, and fluid used, we found similar correlations for all cortisol measures, suggesting that these factors matter less than previously thought (88).

It is possible that the associations between cortisol levels and HCV could be explained by LLD. To date, few studies examined the relationship between LLD, HCV, and HPA axis activity in combination, and those that did (12,57) did not find evidence for a mediating or moderating effect of cortisol, although it is possible that a more nuanced picture emerges when changes in cortisol measures over time are also taken into account, as has been suggested (89). Also, because of the high heterogeneity in etiology of LLD, it is possible that in some subgroups the relationship between HPA axis activity and HCV reduction is stronger than in others.

A limitation of this meta-analysis is that we could not analyze the number and timing of lifetime episodes of depression. However, when we included an additional analysis where we calculated time since first episode based on age of first onset and age at time of MRI for studies reporting this, we found that this was not a significant predictor of HCV.

Another limitation is that age of depression onset was determined by a clinical interview or other self-reported measure. This may have led to information bias, although the direction of this bias may not be straightforward. Self-report of previous episodes may have led to an overestimation of depression episodes in participants currently depressed and an underestimation in control subjects. If so, this will have led to an overestimation of the true effect size of EOD. However, it could also have led to an underestimation if depressed participants underestimated previous depression episodes relative to control subjects. With respect to LOD, it is hard to imagine how the relationship with HCV may have been overestimated, because both cases and control subjects did not report any previous episodes.

A third limitation is that we only included cross-sectional studies, and this meta-analysis therefore cannot determine which comes first: HCV reduction or LLD. Nevertheless, the findings do not seem to support that chronic depression with an early onset leads to reduced HCV later in life, and seem more likely to suggest that reduced HCV, whether caused by prodromal dementia, vascular comorbidity, or other mechanisms, is more apparent in LOD.

In conclusion, this meta-analysis shows that while an overall measure of LLD may be associated with smaller HCVs, differentiating clinical aspects of LLD and examining methodological issues show that this relationship is not straightforward. To increase our understanding of the neurobiological substrate of LLD, future studies should carefully examine the heterogeneity of LLD, in which detailed characterization is made of lifetime history and clinical diagnoses of depression, preferably in large, community-based prospective cohort studies that follow people from adulthood into older age. In addition, studies should examine LLD, brain volumes, HPA axis activity, and risk of dementia in combination.

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