Cerebral microhemorrhage and brain β-amyloid in aging and Alzheimer disease

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ABSTRACT

Objectives: Incidental cerebral microhemorrhage (MH) is frequently found in older individuals scanned with susceptibility-weighted MRI (SWI) or gradient-recalled echo MRI. MH have been linked with β-amyloid (Aβ) deposition using ¹¹C-Pittsburgh compound B (PiB) PET in Alzheimer disease (AD) and cerebral amyloid angiopathy (CAA). We hypothesized that Aβ deposition in asymptomatic elderly individuals is associated with lobar MH (LMH).

Methods: This was a cross-sectional study of 84 elderly healthy controls (HC), 28 subjects with mild cognitive impairment (MCI), and 26 subjects with probable AD who underwent 3-T SWI and ¹¹C-PiB PET. ¹¹C-PiB cortical binding was quantified normalized to cerebellar cortex (standardized uptake value ratio [SUVR]) and scans classified as positive (PiB+), or negative (PiB−) by visual inspection. MH were manually counted and categorized by region and as lobar or nonlobar.

Results: LMH were present in 30.8% of AD, 35.7% of MCI, and 19.1% of HC. The prevalence of LMH among PiB+ subjects was similar, regardless of clinical classification (AD 30.8%, MCI 38.9%, HC 41.4%, p > 0.7). HC with LMH had significantly higher mean neocortical SUVR (1.7 ± 0.5) than HC without LMH (1.3 ± 0.3, p = 0.01). In HC, there was a positive correlation between number of LMH and SUVR, and between LMH and age. In HC, PiB+ (odds ratio [OR] 7.3, 95% confidence interval [CI] 1.6–33.7, p = 0.01) and age (OR 1.2, 95% CI 1.03–1.3, p = 0.02) both independently predicted the occurrence of LMH using logistic regression.

Conclusion: Asymptomatic Aβ deposition in older adults is strongly associated with LMH.

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GLOSSARY

Aβ = β-amyloid; AD = Alzheimer disease; AIBL = Australian Imaging, Biomarkers and Lifestyle Study of Ageing; CAA = cerebral amyloid angiopathy; CAAH = CAA-associated hemorrhage; CDR = Clinical Dementia Rating; CI = confidence interval; HC = healthy controls; ICH = intracerebral hemorrhage; LMH = lobar microhemorrhage; MCI = mild cognitive impairment; MH = microhemorrhage; MMSE = Mini-Mental State Examination; OR = odds ratio; PiB = Pittsburgh compound B; SUVR = standardized uptake value ratio; SWI = susceptibility-weighted MRI.

Cerebral microhemorrhage (MH) can be detected using MRI sequences such as susceptibility-weighted imaging (SWI), sensitive to hemosiderin from the breakdown of blood products, and are frequently found in association with symptomatic intracerebral hemorrhage (ICH), in Alzheimer disease (AD), and also in apparently healthy elderly.

MH have been associated with increasing age, hypertension, diabetes mellitus, male gender, smoking, lacunar infarcts and white matter disease, APOE ε4 alleles, and have been linked with antiplatelet therapy. Deep subcortical MH are generally associated with vascular risk factors, and lobar (particularly posterior) MH (LMH), usually attributed to vascular β-amyloid (Aβ) deposition (cerebral amyloid angiopathy [CAA]).

MH predispose to ICH following ischemic stroke, anticoagulation or antiplatelet therapy, as well as recurrent stroke and recurrent hemorrhage after ICH. They have been...
associated with impaired cognition in otherwise healthy controls, ICH survivors, and reduced survival in memory clinic attendees.

In AD, MH may be relevant to both the manifestation and progression of symptoms, and have also been implicated in complications of AD immunotherapy, particularly in *APOE* ε4 carriers.

PET using 11C-Pittsburgh compound B (PiB) has been used to detect fibrillar Aβ deposition in AD, other neurodegenerative diseases, and in cognitively normal older individuals. Using 11C-PiB, Aβ deposition has been shown in patients with CAA-associated hemorrhage, with hemorrhage post-thrombolysis for ischemic stroke, and topographically, in brain parenchyma corresponding to MH seen with MRI.

This study was performed to assess whether cerebral Aβ deposition is also associated with increased risk of lobar MH (LMH) in asymptomatic individuals.

**METHODS**

**Study population.** Participants of this study were recruited from the Melbourne arm of the Australian Imaging, Biomarkers and Lifestyle Study of Ageing (AIBL). All participants underwent SWI MRI, 11C-PiB PET scan, and blood drawn for biomarkers and *APOE* ε4 genotype sequencing. A total of 138 participants were included in this study: 26 patients with AD, 28 patients with mild cognitive impairment (MCI), and 84 elderly healthy controls (HC). Medical history was obtained from participants or carers, including prescribed antiplatelet or anticoagulant therapy. Vascular risk factors were identified using self-report, physical examination, and laboratory findings: hypertension, hypercholesterolemia, diabetes, current smoking history, atrial fibrillation, prior or current history of vascular disease (coronary or peripheral vascular disease), and dichotomized as present or absent according to published guidelines. Participants with current or past history of stroke were excluded.

**Standard protocol approvals, registrations, and patient consents.** Written informed consent from all participants as well as approval from the Austin Health Human Research Ethics Committee were obtained.

**Clinical assessment.** All participants underwent clinical assessment on the day of PET imaging, including Folstein Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR). Participants diagnosed with AD met National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria for probable AD. Subjects with MCI met Petersen criteria of subjective and objective cognitive difficulties, predominantly affecting memory, in the absence of dementia or significant functional loss.

**PET neuroimaging protocol.** Each subject received ~370 MBq 11C-PiB IV over 1 minute. A 30-minute acquisition, starting 40 minutes after injection of 11C-PiB, was performed using a Phillips Allegro™ PET camera. A transmission scan was performed for attenuation correction. Cortical-to-cerebellar gray matter ratios (standardized uptake value ratio [SUVR]) were generated for regions of interest. Neocortical Aβ-burden (neocortical SUVR) was expressed as the average SUVR of the area-weighted mean of frontal, superior parietal, lateral temporal, lateral occipital, and anterior and posterior cingulate regions. In addition to quantitative analysis, PiB images were read by a nuclear medicine physician with expertise in neuroimaging, blinded to clinical and MRI findings. Subjects were classified as negative, focal, or generalized PiB uptake, according to intensity and extent of cortical binding (figure). A positive PiB scan (PiB+) was defined by visual evidence of focal or generalized cortical PiB binding. Because CAA can affect the cerebellum, we assessed for potential bias from cerebellar Aβ by repeating analyses with SUV normalized to the pons (SUVRpons), and by comparing cerebellar SUVRpons between groups.

**MRI neuroimaging protocol.** MRI was performed on a 3-T Siemens TRIO MRI system. SWI MRI was acquired with 1.0 mm in-plane resolution and 1.75 mm slice thickness, repetition time/echo time of 27/20 msec, and flip angle 20°. In accor-

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**Figure** Susceptibility-weighted MRI with microhemorrhage (A and C, arrows) and 11C-Pittsburgh compound B scan in the same subjects, with Aβ deposition seen as red areas.

The first subject has focal cortical Aβ deposition in the right temporo-occipital cortex, with a normal range neocortical standardized uptake value ratio (SUVR) of 1.49 (B). The second subject has extensive cortical Aβ (D) and a neocortical SUVR of 2.33. Both are asymptomatic healthy elderly subjects.
dance with published guidelines, and in order to avoid misclassification of calcification or diffuse iron deposition in the basal ganglia as MH, MH were identified as round or ovoid (nonlinear) hypointense lesions smaller than or equal to 10 mm (figure). Lesions were tracked through multiple slices to exclude pial blood vessels.33 T1- and T2-weighted images were also available for correlation. All MRI were inspected blind to clinical and PiB scan findings. A consensus was obtained between 2 readers for the number and location of MH on each scan. Location was classified as lobar (LMH+, frontal, parieto-occipital, temporal, and cerebellar) or nonlobar (basal ganglia, brainstem). Cerebellar MH were grouped for analysis as lobar MH. The median time between PiB PET and MRI was 2 weeks.

**Statistical analysis.** Statistical analyses were performed using PASW Statistics SPSS version 18. Differences between groups were assessed with χ², Fisher exact, or Student t tests. In HC participants, Pearson product moment was used to examine for correlation between number of LMH, age, and Aβ burden. Analysis was also performed with LMH by region and corresponding regional SUVR. All analyses were adjusted for demographic factors (age, gender, vascular risk factors, and antiplatelet use). Binary logistic regression was used to assess for independent predictors of presence of LMH. Data are presented as mean ± SD unless otherwise stated.

**RESULTS** Sample demographics. Age, prevalence of vascular risk factors, and antiplatelet use did not differ significantly among the subjects with AD, subjects with MCI, and HC (table 1). Two participants (1 HC, 1 MCI, neither with MH) were taking oral anticoagulation therapy (warfarin) and were included in analyses with those on antiplatelet medication.

All subjects with AD, 64.3% of subjects with MCI, and 34.5% of HC were PiB+ ($\chi^2 p < 0.05$).

**Microhemorrhage topography.** MH were present in 37/138 subjects. The most common loci for MH were parieto-occipital (34.6%), frontal (32.1%), and temporal (13.6%), followed by cerebellar (9.9%), basal ganglia (7.4%), and brainstem (2.5%). There were no significant differences in the regional distribution of lesions between diagnostic groups. There was a trend to increased proportion of MH in posterior regions in PiB+ compared with PiB− subjects, but this did not reach significance (data not shown).

**Lobar microhemorrhage and PiB.** Thirty-four subjects (34/138, 24.6%) had LMH (LMH+). Compared to HC (19.1%), LMH were more prevalent in AD (30.8%) and MCI (35.7%), although the difference was not significant ($\chi^2$ test vs HC: $p = 0.09$ for MCI, $p = 0.24$ for AD). PiB+ HC, MCI, and AD groups all had similar LMH prevalence (table 1), despite significantly higher global PiB burden in AD (mean neocortical SUVR 2.3 ± 0.4) and PiB+ MCI (2.3 ± 0.4) compared with PiB+ HC (1.8 ± 0.3, $p < 0.001$). Four of 55 (7.3%) PiB− HC and 3 of 10 (30%) PiB− subjects with MCI were LMH+.

**Participants with focal PiB retention.** Two subjects with MCI and HC presented with focal PiB retention. Of these, 3 of 6 (50%) had LMH. LMH site corresponded to the region of increased PiB retention in 2 of these cases.

**HCs with LMH.** LMH+ HC presented with higher global PiB retention (neocortical SUVR 1.7 ± 0.5) than LMH− HC (1.3 ± 0.3, $p = 0.01$), and were significantly older (mean age 79.3 ± 5.4 vs 73.5 ± 6.9, $p = 0.001$). While 66.7% of HC with 1 LMH were PiB+, the prevalence was higher (85.7%) in those participants with 2 or more LMH.

There was no significant difference in MMSE, vascular risk, APOE e4 status, or antiplatelet use between LMH+ HC and LMH− HC (table 2).**

**HCs: Pearson correlations.** Increasing age correlated with increasing neocortical SUVR (Pearson $r = 0.33$, $p = 0.003$, adjusted for gender). There was a significant correlation between age and number of LMH ($r = 0.32$, $p = 0.03$), and between neocortical SUVR and number of LMH ($r = 0.27$, $p = 0.02$). There was also a strong correlation between parieto-occipital LMH and parieto-occipital SUVR ($r = 0.28$, $p = 0.01$), but not between frontal LMH and frontal SUVR ($r = 0.09$, $p = 0.43$).

To examine for difference in regional distribution of Aβ between PiB+ HC with and without LMH, we compared ratios of frontal:parieto-occipital

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**Table 1** Demographics, cerebral Aβ, and lobar microhemorrhage

<table>
<thead>
<tr>
<th></th>
<th>HC (n = 84)</th>
<th>MCI (n = 28)</th>
<th>AD (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y, mean ± SD</strong></td>
<td>74.6 ± 6.9</td>
<td>75.9 ± 7.6</td>
<td>74.2 ± 8.6</td>
</tr>
<tr>
<td><strong>Female/male</strong></td>
<td>45/39</td>
<td>14/14</td>
<td>17/9</td>
</tr>
<tr>
<td><strong>MMSE, mean ± SD</strong></td>
<td>29.5 ± 0.7</td>
<td>27.8 ± 2.1a</td>
<td>21.2 ± 5.5a</td>
</tr>
<tr>
<td><strong>CDR, mean ± SD</strong></td>
<td>0.1 ± 0.2</td>
<td>0.4 ± 0.3a</td>
<td>1.0 ± 0.6a</td>
</tr>
<tr>
<td><strong>Vascular risk factors, mean ± SD</strong></td>
<td>2.1 ± 0.8</td>
<td>2.2 ± 1.2</td>
<td>2.0 ± 1.3</td>
</tr>
<tr>
<td><strong>% Antiplatelet Rx</strong></td>
<td>31</td>
<td>39</td>
<td>23</td>
</tr>
<tr>
<td><strong>% APOE e4</strong></td>
<td>32</td>
<td>54b</td>
<td>69b</td>
</tr>
<tr>
<td><strong>Neocortical SUVR, mean ± SD</strong></td>
<td>1.4 ± 0.4</td>
<td>1.9 ± 0.6a</td>
<td>2.3 ± 0.4a</td>
</tr>
<tr>
<td><strong>% PiB+</strong></td>
<td>34.5</td>
<td>64.3b</td>
<td>100b</td>
</tr>
<tr>
<td><strong>% LMH+</strong></td>
<td>All subjects 19.1</td>
<td>35.7</td>
<td>30.8</td>
</tr>
<tr>
<td></td>
<td>PiB+ 41.4c</td>
<td>38.9</td>
<td>30.8</td>
</tr>
<tr>
<td></td>
<td>PiB− 7.3</td>
<td>30.0</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: Aβ = β-amyloid; AD = Alzheimer disease; CDR = Clinical Dementia Rating; HC = healthy elderly controls; LMH = lobar microhemorrhage; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; PiB = Pittsburgh compound B; SUVR = standardized uptake value ratio.

*a* Significantly different from HC, $p < 0.05$ using t test.

*b* Significantly different from HC, $p < 0.05$ using χ².

*c* Significant difference from PiB− HC, Fisher exact $p < 0.001$. 
SUVR. Although there was a trend to greater relative frontal burden in LMH−, this was not significant (LMH− 1.21 ± 0.3, LMH+ 1.15 ± 0.2).

**Logistic regression.** In a logistic regression model, age and PiB+ both independently predicted presence of both MH (any) and LMH in HCs. APOE ε4 carrier status, gender, number of vascular risk factors, and antiplatelet therapy included in the model were not significant predictors (table 3).

Finally, in order to account for potential PiB retention in the cerebellar cortex, analyses were repeated with SUVR generated using thepons as reference region. Cerebellar SUVRpons was similar in HC, subjects with MCI, and subjects with AD (0.51 ± 0.1, 0.50 ± 0.1, and 0.52 ± 0.1, respectively). There was also no significant difference in cerebellar PiB retention between HC with LMH (mean cerebellar SUVRpons 0.52 ± 0.1) and those without LMH (0.50 ± 0.1). There were 6 individu

### Table 2  
**LMH in healthy control subjects**

<table>
<thead>
<tr>
<th></th>
<th>LMH− (n = 68)</th>
<th>LMH+ (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y, mean ± SD</strong></td>
<td>73.5 ± 6.9</td>
<td>79.3 ± 5.4</td>
</tr>
<tr>
<td><strong>Female/male</strong></td>
<td>39/30</td>
<td>7/9</td>
</tr>
<tr>
<td><strong>MMSE, mean ± SD</strong></td>
<td>29.5 ± 0.7</td>
<td>29.4 ± 0.7</td>
</tr>
<tr>
<td><strong>% APOE ε4</strong></td>
<td>30.1</td>
<td>37.5</td>
</tr>
<tr>
<td><strong>% PiB+</strong></td>
<td>25.0</td>
<td>75.00a</td>
</tr>
<tr>
<td><strong>Neocortical SUVR, mean ± SD</strong></td>
<td>1.3 ± 0.3</td>
<td>1.7 ± 0.5a</td>
</tr>
<tr>
<td><strong>Vascular risk factors, mean ± SD</strong></td>
<td>2.1 ± 0.8</td>
<td>1.9 ± 0.6</td>
</tr>
<tr>
<td><strong>% on antiplatelet Rx</strong></td>
<td>30.8</td>
<td>31.3</td>
</tr>
</tbody>
</table>

*Abbreviations: LMH = lobar microhemorrhage; MMSE = Mini-Mental State Examination; PiB = Pittsburgh compound B; SUVR = standardized uptake value ratio.

a Significantly different from LMH−, *p < 0.015 using t test.

b Significantly different from LMH−, *p < 0.02 using Fisher exact test.

### Table 3  
**Binary logistic regression in HC subjects**

<table>
<thead>
<tr>
<th></th>
<th>Any MH (n = 19/84)</th>
<th>Lobar MH (n = 16/84)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>1.2 (1.03–1.3, 0.01)</td>
<td>1.2 (1.03–1.3, 0.02)</td>
</tr>
<tr>
<td><strong>PiB+</strong></td>
<td>5.6 (1.4–22.3, 0.01)</td>
<td>7.3 (1.6–33.7, 0.01)</td>
</tr>
<tr>
<td><strong>APOE ε4 carrier</strong></td>
<td>1.2 (0.3–4.7, 0.8)</td>
<td>0.9 (0.2–4.2, 0.9)</td>
</tr>
<tr>
<td><strong>Antiplatelet Rx</strong></td>
<td>0.8 (0.2–3.3, 0.8)</td>
<td>0.4 (0.1–1.8, 0.2)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>2.1 (0.6–7.4, 0.3)</td>
<td>2.7 (0.7–10.9, 0.2)</td>
</tr>
<tr>
<td><strong>Vascular risk factor score</strong></td>
<td>0.7 (0.3–1.7, 0.4)</td>
<td>0.5 (0.2–1.4, 0.2)</td>
</tr>
</tbody>
</table>

*Abbreviations: CI = confidence interval; HC = healthy controls; MH = microhemorrhage; PiB = Pittsburgh compound B.*

**DISCUSSION** Using fine-slice, high-sensitivity SWI MRI, cerebral MH are a frequent finding in the cognitively normal elderly population. This study identified lobar MH in 30.8% of subjects with AD, 35.7% of subjects with MCI, and 19.1% of HC, slightly higher than previous reports of prevalence ranging from 12.5% to 32% in subjects with AD and 0% to 12% in HC. The higher prevalence in our study may be the result of dissimilarities in demographics, the classification of MH, or the imaging protocol. SWI MRI thin-slice imaging provides better contrast and higher sensitivity for detection of MH, with up to threefold higher yield than conventional gradient echo MRI.1

The prevalence of cortical 11C-PiB retention reported here is well in agreement with previous reports, reflecting a continuum of increasing prevalence of cerebral Aβ-burden with age in individuals without dementia.33 However, as 11C-PiB binds to Aβ deposits in both gray matter and vessel walls,34 their relative contribution to the PET signal remains unclear. The majority of patients with AD have some degree of CAA, and about a quarter have extensive CAA at postmortem,35 whereas in one study, one-fifth of subjects with CAA-associated hemorrhage (CAAH) at postmortem had no senile plaques.36

Evidence suggests that even without plaques, 11C-PiB scans are likely to be positive in CAA.37,38 Increased 11C-PiB binding has been shown surrounding sites of MH on coregistered MRI,37 and in 2 studies, global cortical 11C-PiB retention in subjects with CAAH has been found to be in the middle range between HC and AD.25,24 In agreement with these reports, we found that LMH+ HC presented with intermediate Aβ burden, with values in between those observed in LMH− HC and subjects with AD. However, without histopathologic correlation it is not clear if the 11C-PiB binding in these subjects is attributable to vessel deposits, plaque, or both.

It has been suggested that the regional pattern of Aβ may separate the 2 processes. At postmortem, the occipital lobes appear frequently involved in cases of CAA, but are relatively less affected by neuritic plaques than other brain regions in AD.39 These findings have been paralleled more recently using 11C-PiB PET, with proportionally slightly higher occipital PiB retention (relative to global) in cases of probable CAA compared with AD.24,25 Our results in
cognitively normal individuals are also consistent with these findings, with correlations between PiB retention and LMH in the parieto-occipital region, but not in the frontal area. There was also a trend to differing proportional PiB distribution (frontal: parieto-occipital) between PiB+ HC with and without LMH, but this did not reach statistical significance.

In HCs, a positive PiB scan and increasing age were independent predictors of the presence of lobar MH, in a model including gender, APOE ε4 status, vascular risk factors, and antiplatelet therapy. While there were trends to higher prevalence of LMH among APOE ε4 carriers in our study, this did not reach significance, and APOE ε4 status was not a significant independent predictor of LMH in regression models. Although APOE ε4 may predispose to increased risk of CAA in the general population, in this study it was the presence of Aβ, rather than APOE ε4, that was of greater significance.

LMH were present in 31% to 41% of all PiB+ subjects (AD, MCI, and HC), suggesting that the risk of LMH—and, as a consequence, symptomatic intracerebral bleeding—may be similarly increased in all PiB+ individuals, irrespective of their clinical classification. These findings may ultimately have implications for stratification of antiplatelet, anticoagulant, and thrombolytic therapy in the wider community.

In a cohort of cognitively normal individuals with no prior history of cerebrovascular disease, 67% of participants with 1 LMH and 86% with 2 or more were PiB+. These results provide support for the use of the Boston Criteria for identification of CAA in this population.

In some AD anti-Aβ immunotherapy trials, individuals with MH are excluded due to the possibility of vascular complications such as vasogenic edema. Our results show that 3–4 out of 10 individuals with high Aβ burden have LMH. Clear justification for exclusion of such patients from immunotherapy trials is essential as it may subsequently exclude a significant proportion of patients from this form of therapy.

This study has some limitations. First, our sample had a higher proportion of APOE ε4 carriers compared with the general population, and was largely composed of a middle-class, Caucasian demographic. As per the wider AIBL protocol, individuals with a history of ischemic stroke, ICH, or head injury were excluded, as well as those with a history of alcohol dependence. This, and a high proportion of treated vascular risk factors among the participants, may explain the lower prevalence of nonlobar MH in this study compared with some previous reports, and limit applicability to wider, sociodemographically diverse populations. Second, while low-level vascular Aβ in the cerebellar cortex could affect SUVR measurements, we found no differences in the results of all analyses when repeated using thepons instead of the cerebellar gray matter as the reference region nor cerebellar SUVRpons between participants with or without LMH.

Lobar microhemorrhages are a not-infrequent finding in cognitively normal older individuals, and are strongly associated with the presence of Aβ and increasing age. This may have important implications for selection and risk stratification of individuals undergoing antiplatelet, anticoagulant, and thrombolytic therapies, as well as anti-amyloid therapies in the future.

**AUTHOR CONTRIBUTIONS**

P.Y.: principal/corresponding author, PET analysis, data analysis, author of manuscript. R.S.: MRI analysis, revision of manuscript. V.L.V.: PET analysis, revisions of manuscript. S.F.: conduct of MRI, revision of manuscript regarding MRI parameters. C.M.: revisions of manuscript. C.C.R.: principal investigator of parent study, MRI and PET analysis, revisions of manuscript.

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DISCLOSURE

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REFERENCES


**Historical Abstract: December 8, 2009**

SLEEP APNEA IN YOUNG ABSTINENT RECREATIONAL MDMA (“ECSTASY”) CONSUMERS
Una D. McCann, Francis P. Sgambati, Alan R. Schwartz, George A. Ricaurte

**Background:** Methylenedioxymethamphetamine (MDMA, “ecstasy”) is a popular recreational drug of abuse and a selective brain serotonin neurotoxin. Functional consequences of MDMA neurotoxicity have defied ready characterization. Obstructive sleep apnea (OSA) is a common form of sleep-disordered breathing in which brain serotonin dysfunction may play a role. The present study sought to determine whether abstinent recreational MDMA users have an increased prevalence of OSA.

**Methods:** We studied 71 medically healthy recreational MDMA users and 62 control subjects using all-night sleep polysomnography in a controlled inpatient research setting. Rates of apneas, hypopneas, and apnea hypopnea indices were compared in the 2 groups, controlling for body mass index, age, race, and gender.

**Results:** Recreational MDMA users who had been drug free for at least 2 weeks had significantly increased rates of obstructive sleep apnea and hypopnea compared with controls. The odds ratio (95% confidence interval) for sleep apnea (mild, moderate, and severe combined) in MDMA users during non-REM sleep was 8.5 (2.4–30.4), which was greater than that associated with obesity [6.9 (1.7–28.2)]. Severity of OSA was significantly related to lifetime MDMA exposure.

**Conclusions:** These findings suggest that prior recreational methylenedioxymethamphetamine use increases the risk for obstructive sleep apnea and lend support to the notion that brain serotonin neuronal dysfunction plays a role in the pathophysiology of sleep apnea.

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Comment from Robert A. Gross, MD, PhD, FAAN, Editor-in-Chief: It’s not often that a “natural experiment” produces interpretable results that are informative of pathophysiology. This one does.