Statin use is associated with reduced depressive symptoms in Europeans, but increased symptoms in ethnic minorities in UK: An observational study

E D Williams, Senior Research Fellow, UCL Institute of Cardiovascular Science, University College London.

S V Eastwood, Clinical Research Fellow, UCL Institute of Cardiovascular Science, University College London.

T Tillin, Senior Research Fellow, UCL Institute of Cardiovascular Science, University College London.

R Stewart, Professor of Psychiatric Epidemiology & Clinical Informatics, Institute of Psychiatry, King's College London.

N Chaturvedi, Professor of Clinical Epidemiology, UCL Institute of Cardiovascular Science, University College London.

A D Hughes, Professor of Cardiovascular Physiology and Pharmacology, UCL Institute of Cardiovascular Science, University College London.

Submitting and corresponding author: Emily D Williams, email: emily.williams@ucl.ac.uk.

Running head: Statin use, depression and ethnicity

Keywords: Statins; depression; risk factors; ethnic differences

Word count: 806 (including references)

Numbers of tables: 1

To the Editor: Proposed as potential mood-enhancing therapy [1], evidence linking statin use with depression remains conflicting [2]. Marked ethnic differences exist in rates of CVD, depression, and responses to some drugs [3,4], and yet ethnic minority groups (EMGs) have been under-represented in statin trials and no studies have examined ethnic differences in the statin-depression relationship.

Cross-sectional data from a population-based tri-ethnic study [5] were available on 638 White Europeans, 487 South Asians and 208 African-Caribbeans. Depression (score of ≥4/10 on the ethnically-validated Geriatric Depression Scale [6]), and other psychosocial, behavioural, anthropometric and medication history data were collected. Statin use was identified by prescription from participant/GP records (as were CVD and hypertension). Diabetes was identified from medical record, diagnosis recall, or OGTT [5].

Statin use was modelled as a predictor for depression in logistic regression analyses, with ethnicity by statin use interaction terms included. Models were also stratified by ethnicity. In a 77% male sample (mean age=70), 56% of participants were receiving statins (48% White European, 68% South Asian, 52% African-Caribbean). Of those on statins, South Asian and African-Caribbean participants were significantly more likely to report depression compared with Europeans (OR 2.00 (95% CI 1.25-3.21) and 2.96 (1.67-5.24), respectively). The similar relationship between statin use and depression in South Asians and African-Caribbeans (Table 1♦) meant their data were pooled. In ethnically-stratified model 1, statin use was not related to depression in Europeans, whereas among EMGs, depression was significantly higher in people on statins (full sample: ethnicity-statin interaction p=0.11). After full adjustment, analyses showed a non-significant trend towards a protective effect of statin use on depression in Europeans and a deleterious effect in EMGs (full sample: ethnicity-statin interaction,p=0.041).

A few explanations could exist for this differential relationship between statin use and depression. *'Presentation bias'* (different presentation of depression by a particular ethnic group to healthcare professionals could increase the likelihood of detection/treatment of other conditions) was explored with depression somatisation, by correlating depressive symptoms with self-reported health. No group demonstrated elevated depression somatisation, with the same strength and direction of relationship observed across all groups. Depression was measured using a screening tool rather than clinical diagnosis;

often a study limitation, here it reduced 'presentation bias' likelihood, since depression may not have been discussed with GPs.

Another possibility is that the statin-depression association was *confounded* by CVD due to the established bi-directional relationship between depression and CVD. To examine whether, among EMGs, depression is a stronger predictor of CVD or vice versa, we adjusted for CVD in the main models (4-5) and stratified the fully-adjusted model by CVD status in sensitivity analyses. The same results were observed across groups irrespective of CVD prevalence (results not shown), indicating that the statin-depression link did not result from statin use acting as a proxy for CVD.

Therefore, our results may reflect a *true ethnic difference* in the impact of statins on depression. Ethnic differences in response to statins could elicit direct and indirect effects on depression, i.e. across ethnicities, there could be a differential influence of statins on lipid sub-fractions or of statins' protective effects on cerebrovascular processes, both of which could impact mood. Alternatively, EMGs could be more vulnerable to statin-induced side-effects, influencing depression.

EMGs receiving statins in this sample were over twice as likely to report depression as Europeans. To our knowledge, this is the first study to examine ethnic differentials in the statin-depression relationship. We acknowledge our dataset's limitations, in particular its cross-sectional nature precluding causal interpretations and limited study power; however our aim is to highlight these findings and urge others to interrogate existing clinical trial/healthcare databases, as well as including sufficient EMG numbers in future studies. Given the pervasiveness of statins and predisposition towards CVD and depression among certain groups [3,4], this finding has potentially serious implications for the mental health of thousands of EMGs being treated with statins.

COMPETING INTERESTS: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations

that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

ACKNOWLEDGEMENTS: We acknowledge the contribution of the SABRE research team and participants. The SABRE study was supported by Diabetes UK, Wellcome Trust, British Heart Foundation (BHF) and the Medical Research Council. RS is part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London.

REFERENCES

1. O'Neil A,Sanna L,Redlich C,Sanderson K,Jacka F,Williams LJ,Pasco JA, Berk M. The impact of statins on psychological wellbeing:a systematic review and meta-analysis. BMC Med. 2012;10:154.

2. While A,Keen L. The effects of statins on mood:a review of the literature. Eur J Cardiovasc Nurs 2012;11:85-96.

3. Tillin T,Hughes AD,Mayet J,Whincup P,Sattar N,Forouhi N,McKeigue PM,Chaturvedi N. The relationship between metabolic risk factors and incident cardiovascular disease in Europeans, South Asians and African Caribbeans. JACC. 2013;61:1777-86.

4. Weich S,Nazroo J,Sproston K,Mcmanus S,Blanchard M,Erens B,Karlsen S,King M,Lloyd K, Stansfeld S, Tyrer P. Common mental disorders and ethnicity in England:the EMPIRIC Study. Psychol Med. 2004;34:1543-51.

5. Tillin T,Forouhi NG,McKeigue PM,Chaturvedi N. Southall And Brent REvisited:Cohort profile of SABRE, a UK population-based comparison of cardiovascular disease and diabetes in people of European, Indian Asian and African Caribbean origins. Int J Epidemiol. 2012;41:33-42.

6. D'Ath P,Katona P,Mullan E,Evans S,Katona C. Screening, detection and management of depression in elderly primary care attenders. I:The acceptability and performance of the 15 Item Geriatric Depression Scale and the development of short versions. Family Pract. 1994;11:260-6.

Table 1: Risk of major depression according to statin use across ethnic groups

	White European (n = 638)	South Asian and African Caribbean[π] (n = 695)
Not on statins - % depressed	9.6	11.9
On statins - % depressed	9.8	19.5*

	Risk of depression according to statin use		Ethnic-statin interaction
	OR (95% CI)		*p* value
Model 1: age and sex	1.03 (0.60-1.76)	1.91 (1.22-3.01)[♦]	0.11
Model 2: model 1 + manual labour and stressful life events	0.96 (0.56-1.65)	1.89 (1.20-2.99)	0.087
Model 3: model 1 + smoking, alcohol intake and physical activity	0.84 (0.47-1.49)	1.81 (1.14-2.87)	0.085
Model 4: model 1 + BMI, diabetes, hypertension and CVD	0.58 (0.29-1.15)	1.66 (0.98-2.83)	0.036
Model 5: Full adjustment	0.54 (0.26-1.13)	1.67 (0.97-2.88)	0.041
In sample with total cholesterol > 3mmol/L[Σ]:			
Full adjustment	0.52 (0.24-1.13)	1.60 (0.91-2.79)	0.049

significant ethnic group difference of $p<0.05$. BMI: body mass index. CVD: cardiovascular disease. [π] South Asians only: % depressed - Not on statins=10.2%, on statins=17.9%. For African Caribbeans only: % depressed - Not on statins=14.6%, on statins=24.8%*. [♦] South Asians only: OR 1.94 (1.07-3.52), $p=0.13$ for ethnic-statin interaction. African Caribbeans only: OR 2.19 (1.05-4.57), $p=0.16$ for ethnic-statin interaction. [Σ] To assess the potential confounding role of very low cholesterol, the sample was restricted to those participants with total cholesterol of >3mmol/L.