ISSN 1948-9358 (online)

World Journal of *Diabetes*

World J Diabetes 2017 June 15; 8(6): 230-310

Published by Baishideng Publishing Group Inc

World Journal of Diabetes

Contents

Monthly Volume 8 Number 6 June 15, 2017

NAME OF JOURNAL
World Journal of Diabetes

ISSN
ISSN 1948-9358 (online)

LAUNCH DATE
June 15, 2010

FREQUENCY
Monthly

EDITORIAL OFFICE
Xiu-Xia Song, Director
World Journal of Diabetes
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
June 15, 2017

World Journal of Diabetes

Submit a Manuscript: http://www.f6publishing.com

World J Diabetes 2017 June 15; 8(6): 286-296

DOI: 10.4239/wjd.v8.i6.286

ISSN 1948-9358 (online)

ORIGINAL ARTICLE

Observational Study

Statin use and cognitive function in middle-aged adults with type 1 diabetes

Karen A Nunley, Trevor J Orchard, Christopher M Ryan, Rachel Miller, Tina Costacou, Caterina Rosano

Karen A Nunley, Trevor J Orchard, Christopher M Ryan, Rachel Miller, Tina Costacou, Caterina Rosano, Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA 15213, United States

Author contributions: Nunley KA, Orchard TJ, Costacou T and Rosano C contributed to study conception and design; Nunley KA, Ryan CM, Miller R and Costacou T contributed to data acquisition, analysis, and interpretation; Nunley KA, Orchard TJ, Ryan CM, Miller R, Costacou T and Rosano C contributed to writing, editing, reviewing, and final approval of manuscript.

Supported by National Institutes of Health (NIH) National Institute of Diabetes and Digestive and Kidney Disorders (NIDDK) grants, Nos. R01 DK089028, PI (to Rosano C); R37 DK034818-25, PI (to Orchard TJ); and R21 DK082900, PI (to Costacou T).

Institutional review board statement: The study was reviewed and approved by the University of Pittsburgh Institutional Review Board.

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: No authors report a conflict of interest.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

Correspondence to: Karen A Nunley, PhD, MS, Visiting Assistant Research Professor, Department of Epidemiology, University of Pittsburgh, 5138 South Parran Hall, 130 N De Soto St., Pittsburgh, PA 15213, United States. kan62@pitt.edu
Telephone: +1-412-3833913
Fax: +1-412-6247397

Received: November 4, 2016
Peer-review started: November 6, 2016
First decision: November 30, 2016
Revised: February 17, 2017
Accepted: May 3, 2017
Article in press: May 5, 2017
Published online: June 15, 2017

Abstract

AIM

To test associations between statin use and cognitive impairment in adults with childhood-onset type 1 diabetes (T1D).

METHODS

In 2010-13, *n* = 108 middle-aged participants from ongoing observational Pittsburgh Epidemiology of Diabetes Complications Study underwent neurocognitive assessment (mean age and T1D duration of 49 and 41 years, respectively). All were diagnosed with childhood-onset (*i.e.*, prior to age 18) T1D between 1950 and 1980 and were seen within one year of diagnosis at Children's Hospital of Pittsburgh. Self-reported statin use (yes/no and if yes, name of statin) was collected biennially from parent study baseline (1986-1988) to time of neurocognitive testing. Logistic regression models tested associations between statin use groups and cognitive impairment (defined as having two or more cognitive test scores 1.5SD or worse than published norms) while linear regression models tested associations between statin use groups and cognitive domain z-scores (domains: Verbal IQ, memory, executive function, psychomotor speed, and visuo-

construction). All models controlled for education and age. To address confounding by indication, models were repeated using a propensity score for statin use.

RESULTS

Of the 108 participants, 51 reported never using statins. Median duration of statin use among the 57 ever users was 6 years. These 57 ever statin users were split to create two groups (⩽ or > median years of statin use): 1-6 years (n = 25), and 7-12 years (n = 32). Compared with never users, using statins 1-6 years tripled the odds of cognitive impairment (OR = 3.16; 95%CI: 0.93-10.72; P = 0.06) and using statins 7-12 years almost quintupled the odds of cognitive impairment (OR = 4.84; 95%CI: 1.63-14.44; P = 0.005). Compared with never users, using statins 1-6 or 7-12 years was related to worse performance in the memory domain (β = -0.52; P = 0.003, and -0.39; P = 0.014, respectively). Adjusting for coronary artery disease, low density lipoprotein cholesterol, and *Apo E4* status did not substantially alter results, and none of these covariates were significantly related to cognitive outcomes (all P > 0.05). Propensity score analyses support that associations between poor cognitive outcomes and statin use were not due merely to confounding by indication.

CONCLUSION

Statin use was associated with cognitive impairment, particularly affecting memory, in these middle-aged adults with childhood-onset T1D, whom at this age, should not yet manifest age-related memory deficits.

Key words: Type 1 diabetes; Cognitive impairment; Memory; Statin use; Cohort study

Core tip: Animal and cell culture studies show that statins can damage cerebral gray and white matter, thereby affecting cognitive function. Findings from human studies remain controversial; early observational studies reported that statin use negatively affected cognition, especially memory, while more recent studies have not replicated these findings. Even though statins are widely prescribed for people with type 1 diabetes (T1D), only one study to date has examined whether statin use is related to cognitive impairment in this patient population. We propose that deleterious effects statins may exert on cognition may be more pronounced in people with T1D, as these individuals are already at an increased risk of cognitive impairment due to long-term exposure to metabolic dysregulation.

Nunley KA, Orchard TJ, Ryan CM, Miller R, Costacou T, Rosano C. Statin use and cognitive function in middle-aged adults with type 1 diabetes. *World J Diabetes* 2017; 8(6): 286-296 Available from: URL: http://www.wjgnet.com/1948-9358/full/v8/i6/286.htm DOI: http://dx.doi.org/10.4239/wjd.v8.i6.286

INTRODUCTION

Whether statins negatively affect cognitive function remains under dispute. Goldstein and Mascitelli[1] (2014) propose that statins may negatively affect the brain and cognitive health, potentially *via* impaired myelination. Additionally, cell culture and animal studies show that statins exert neurotoxic effects[2,3]. Four recent meta-analyses/reviews, however, found no significant relationship between statin use and cognitive impairment[4-7]. While these reviews do acknowledge that statins may negatively impact cognitive function in "vulnerable" populations, they provide no insight as to who may be "vulnerable". We raise the possibility that adults living with type 1 diabetes (T1D) since childhood may fit this "vulnerable" category, for at least two reasons.

First, a growing body of literature recognizes the deleterious effects of T1D on brain structure, with smaller total brain volume reported among those with than those without T1D[8-10]. Perhaps negative effects of statins of brain function are more pronounced in those with overall smaller brain volume. In other words, those with greater cerebral gray and white matter volumes may be more able to compensate for insults to cerebral gray or white matter related to statin use.

Second, to minimize cardiovascular events, the American Diabetes Association recommends moderate to high intensity statin treatment for diabetic patients at any age who also have atherosclerotic cardiovascular disease, or its risk factors (*e.g*., hypertension, dyslipidemia, overweight/obese), and for all diabetic patients aged 40 years and older, regardless of cardiovascular risk[11]. This means that many T1D patients begin using statins in early adulthood, often before age 30, whereas statin use is relatively uncommon among otherwise "healthy" adults under age 45. While youth with neurofibromatosis 1 or familial hypercholesterolemia also use statins at an early age, the long-term effects of statin use on cognitive function in these patients also remains unclear[12]. In fact, a recent randomized controlled trial recommends against using simvastatin to enhance cognitive function in children with neurofibromatosis 1[13]. Age at initial statin exposure is an important consideration because the brain's white matter continues to undergo myelination well into the 4th decade of life[14,15]. If statins do compromise myelin integrity, then statin use may differentially impact the brain depending on the age at which statin use begins. Additionally, long-term statin use may also reduce the number of glial progenitor cells available for future recruitment as these patients age[16]. Thus, exposure to statins prior to age 40 years, in combination with the metabolic dysregulation that accompanies T1D, may noticeably disrupt brain myelination or myelin integrity, whereas little to no discernable disruption of brain myelin/myelination occurs when delaying exposure to statins until after age 50, and/or in the absence of T1D.

Despite this unique statin use prolife of T1D patients, we found only one study to examine statins and cogni-

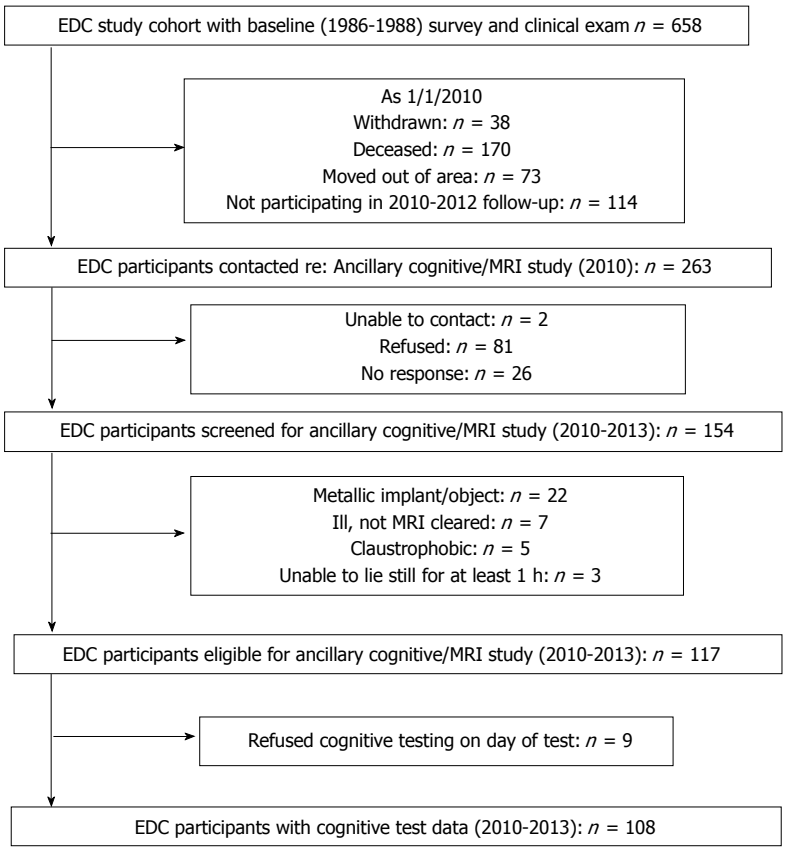

Figure 1 Recruitment of participants with type 1 diabetes from the parent Pittsburgh Epidemiology of Diabetes Complications Study into the ancillary neurocognitive study. EDC: Epidemiology of Diabetes Complications.

tive function in adults with T1D[17]. This small study found no association between statin use and cognitive impairment. However, only 11 out of 55 cases used statins, and duration of statin use was not examined.

We recently documented a higher-than-expected prevalence of cognitive impairment in the middle-aged T1D cohort currently being reported[18], but did not examine statin use as a risk factor for cognitive impairment. This cross-sectional study was therefore conducted to determine whether statin use was associated with cognitive impairment in middle-aged adults with childhood-onset T1D.

MATERIALS AND METHODS

Participants

This study sample was recruited from the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study, an on-going, prospective observational study of individuals diagnosed with childhood-onset (< age 17 years) T1D between 1950 and 1980, and drawn from the Children's Hospital of Pittsburgh diabetes registry. During 2010-2013, an MRI eligible subset (108 out of 261 living in the Pittsburgh area, Figure 1) participated in an ancillary neuroimaging and neurocognitive study.

Cognitive assessment

Details and results comparing cognitive impairment between this T1D cohort and 138 similarly-aged adults without T1D have been previously published (Nunley *et al*[18], 2015). In brief, both cohorts underwent a neurocognitive test battery to assess verbal IQ (North American Adult Reading Test); memory [Rey Auditory Verbal Learning Test - immediate, delay and interference trials, Rey-Osterrieth Complex Figure Delay Task (ROCF-Delay), and Four Word Short Term Memory 5-, 15- and 3-s lists]; executive function [Verbal Fluency F-A-S (FAS), Stroop Color-Word (Stroop-CW), Trails Making B (TMTB), Ratio TMTB: TMTA, Letter-Number Sequence]; psychomotor speed [Digit Symbol Substitution Test (DSST), Grooved Pegboard (GP), Trail Making Test A (TMTA)]; semantic fluency [Verbal Fluency Animals (Animals)]; and visuo-construction [Rey-Osterrieth Complex Figure Copy Task (ROCF-copy)]. In addition to calculating standardized scores for each domain, raw scores on each task were compared to published, demographically-appropriate means[19-21]. T1D cases performed significantly worse than non-T1D controls on seven tasks: FAS, TMTB, DSST, GP, Stroop-CW, Animals, and ROCF-copy. Any participant scoring 1.5 SD or worse than demographically-appropriate published norms on two or more of these seven tasks met the study definition of cognitive impairment[18]; this classification of cognitive impairment (scores worse than 1.5SD) has been previously validated[22].

Statin use

Participants self-reported all medication use biennially, from parent study baseline (1986-1988) through time of cognitive testing (2010-2013). Statin type was determined using Anatomical Therapeutic Chemical Classification System coding (ATC code): ATC codes

C10AA01, 02, and 05, or combination drugs using simvastatin, atorvastatin, or lovastatin, were classified as lipophilic, while codes C10AA03, 04 and 07, or combination drugs using pravastatin or rosuvastatin, were classified as hydrophilic.

Depression/depressive symptoms

Participants completed the Beck Depression Inventory at time of cognitive testing; scores $\geqslant$ 10 were categorized as positive for depressive symptoms[23].

Risk factors

Serum total and HDL cholesterol levels were assessed, using standardized methods, at each clinic visit from parent study baseline (1986-1988) to time of cognitive testing (2010-2013); low density lipoprotein cholesterol (LDLc) was calculated using the Friedwald equation. Details on methods of assessing lifestyle/medical factors (*e.g.*, blood pressure, diabetes complications, inflammatory markers) have been described elsewhere (for details, see Pambianco *et al*[24], 2006).

Brain imaging markers

Severity of cerebral white matter hyperintensities (Fazekas rating 2-3 *vs* Fazekas 1) served as markers of cerebral small vessel disease; for details of image acquisition and rating of white matter hyperintensities, see Nunley *et al*[25], 2015. Left hippocampal volume, as a percentage of total intracranial volume, was chosen for these analyses as hippocampal volume is positively related to memory performance; for details of gray matter imaging and segmentation, see Hughes *et al*[26], 2013.

Statistical analysis

Participants with neurocognitive data (n = 108) were compared with the remaining 154 participants from the parent study who were MRI ineligible, unable to schedule, or not interested in the neurocognitive study. Data from the parent study's 2004-2006 exam were used to compare participant characteristics, including statin use (yes/no). This time point was selected because it was the most recent physical exam for participants who did not participate in neurocognitive study (*i.e.*, only the subgroup participating in the neurocognitive exam underwent a physical exam in 2010-2013, while all participants were offered a physical exam in 2004-2006).

Participants with neurocognitive data were categorized into three groups, based on the distribution of duration of statin use: Never (0 years); 1-6 years; and 7-12 years. This created two groups of ever statin users, split by the median years of statin use. Lipophilic statin use was also determined for all statin users. Characteristics of the three groups were compared using ANCOVA, Fisher exact test, and Jonckheere-Terpstra test as appropriate. *T* tests, Fisher exact, and Wilcoxon Rank-Sum tests compared select factors between participants by cognitive impairment status, as appropriate. Age- and education-adjusted *P* values were obtained from ordinal logistic regression models.

Logistic and linear regression models tested the association between statin use (covariate of interest, with never users as the referent group) and cognitive impairment or cognitive domain z-scores (outcomes). All models controlled for age and education, as we previously demonstrated that education was highly associated with cognitive impairment in this cohort[18]. Each candidate explanatory factor (*i.e.*, related to statin use with a $P \leqslant 0.10$) was entered individually into the model(s); this approach was necessary due to the high degree of multicollinearity between most factors. Underlying brain pathology markers (white matter hyperintensity severity, left hippocampal volume) were forced separately into the models. To arrive at the most parsimonious models, only factors associated with the outcome at $P \leqslant 0.05$ were retained and presented in the tables, controlling for age and education.

Lastly, to account for possible confounding by indication and given the limited sample size of the study, we calculated a propensity score covariate to control for the group difference in statin use. The propensity score was generated based on multinomial logistic regression with the following covariates: Diastolic blood pressure, LDLc, body mass index, smoking history, and history of high blood pressure/using anti-hypertensive medications. Relationships between duration of statin use with cognitive impairment and memory domain z-score were then assessed by logistic regression and linear regression, respectively, while adjusting for the propensity score, age and education.

All participants provided informed consent prior to all study procedures. The University of Pittsburgh IRB approved the study. SAS 9.3 (Cary, NC) was used for data analyses. A biostatistician from University of Pittsburgh Medical Center, Dr. Yuefang Chang, was consulted and contributed to the statistical analyses for this study.

RESULTS

Statin use, duration of statin use, study-average LDL cholesterol, history of high blood pressure, and glycemic control did not differ significantly between those who participated in the neurocognitive study and those unable, ineligible, or refusing participation in the ancillary neurocognitive study (Table 1, all $P > 0.10$). Those who agreed to participate had marginally shorter diabetes duration and were generally healthier (*e.g.*, lower prevalence rates of retinopathy, neuropathy, microalbuminuria, coronary artery disease) than those who did not participate (Table 1, all $P < 0.02$).

Of the 108 with cognitive data, a single participant first reported statin use in 1990-1992; a second participant reported statin use in 1996-1998. Statin use increased at each successive biennial exam, with a total

Table 1 Adults with type 1 diabetes from the Pittsburgh Epidemiology of Diabetes Complications Study, by participation status in the ancillary neurocognitive study

	Non-participant (*n* = 154)	Participant (*n* = 108)	*P* value
Demographic and lifestyle factors, data are *n* (%), mean ± SD, or median (IQR)			
Age (yr)	51.17 ± 7.74	49.52 ± 7.04	0.08
Female	86/136 (63%)	55 (51%)	0.07
Years of education	14 ± 2	15 ± 3	0.05
Ever smoking 100 + cigarettes[1]	57/136 (42%)	41 (38%)	0.60
ApoE4 (24, 34, 44)	34/151 (23%)	34 (32%)	0.12
BMI (kg/m^2)	27.52 ± 4.88	26.74 ± 4.26	0.20
Depressive symptoms[2]	45/128 (35%)	23/100 (23%)	0.06
Physical activity (Kcal)[3]	729 (308-1663)	1009 (448-1966)	0.05
Type 1 diabetes-related factors			
T1D duration (yr)	37.14 ± 7.20	35.50 ± 6.32	0.07
Age at diagnosis (yr)	8.62 ± 4.10	8.28 ± 4.11	0.51
HbA1c (%)	7.69 ± 1.69	7.85 ± 1.85	0.51
A1c months (AU)	1036.38 ± 481.55	966.82 ± 382.02	0.21
Insulin sensitivity (eGDR, mg/kg per minute)	7.65 ± 2.11	7.68 ± 2.47	0.94
eGFR (mL/min per 1.73 m^2)	77.49 ± 24.41	83.31 ± 24.06	0.09
Proliferative retinopathy	85/131 (65%)	51/107 (48%)	0.009
Microalbuminuria	98/133 (74%)	54/92 (59%)	0.02
Coronary artery disease	48 (31%)	18 (17%)	0.009
Cardiac autonomic neuropathy	89/125 (71%)	48/97 (49%)	0.001
Distal symmetric polyneuropathy	86/128 (67%)	52/100 (52%)	0.02
Cardio-metabolic factors			
Systolic blood pressure (mmHg)	116 ± 17	114 ± 16	0.28
Diastolic blood pressure (mmHg)	65 ± 10	66 ± 11	0.42
History of high blood pressure[4]	71 (46%)	39 (36%)	0.13
Total cholesterol (mg/dL)	174.07 ± 34.92	174.79 ± 35.85	0.88
LDL cholesterol (mg/dL)	98.15 ± 28.44	98.48 ± 33.72	0.94
HDL cholesterol (mg/dL)	59.89 ± 16.31	60.63 ± 16.68	0.74
Serum creatinine (mg/dL)	1.12 ± 0.67	1.07 ± 0.61	0.57
Ever used statins[1]	97 (63%)	57 (53%)	0.13
Years of statin use[1]	3 (0-6)	2 (0-8)	0.44
Study average LDLc (mg/dL)[1]	109.95 ± 23.28	107.65 ± 25.96	0.45
Inflammatory markers			
WBC × 10^3/mm^2	6.2 (4.9-7.8)	6.1 (5.2-6.9)	0.30
Adiponectin (μg/mL)	21.1 (15.2-31.0)	22.2 (15.2-30.1)	0.83
IL-6 (ng/mL)	1.4 (0.8-2.3)	1.3 (0.8-1.8)	0.42
TNFα (pg/mL)	1.3 (1.0-1.9)	1.3 (1.0-1.8)	0.92
C-reactive protein (mg/L)	1.7 (0.9-3.3)	1.1 (0.6-2.5)	0.03

[1]Assessed repeatedly from 1986-88 (baseline) through 2004-2006; [2]Beck Depression Inventory score ⩾ 10; [3]Estimated self-reported weekly activity per modified Paffenbarger questionnaire; [4]Blood pressure > 140/80 at any physical exam as part of the parent study and/or any self-reported use of anti-hypertensive medication (1986-2006). Factors assessed in 2004-2006 unless otherwise specified. T1D: Type 1 diabetes; LDLc: Low density lipoprotein cholesterol; BMI: Body mass index; eGDR: Estimated glucose disposal rate; WBC: White blood cell count; IL-6: Interleukin-6; TNFα: Tumor necrosis factor alpha.

of 57/108 classified as "ever" statin users (Figure 2). Of ever statin users, 51/57 (89%) used only lipophilic statins; the small number using hydrophilic statins did not allow for meaningful comparisons by statin type.

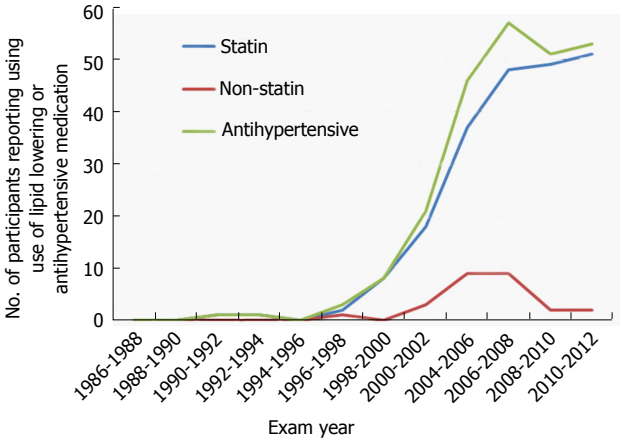

Figure 2 Numbers of participants with type 1 diabetes in the ancillary neurocognitive study (*n* = 108) who reported using lipid lowering and antihypertensive medications from parent study baseline (1986-1988) through time of cognitive assessment (2010-2012).

Of the 51 "never" statin users, six individuals reported using a non-statin alternative (*e.g.*, nicotinic acid) to control their cholesterol.

The three statin use groups did not significantly differ (Table 2, all $P > 0.05$) in male:female ratio, education, *ApoE4* allele status, estimated weekly physical activity, presence of depressive symptoms, age at T1D diagnosis, serum glucose at time of cognitive testing, prevalent cardiac autonomic neuropathy, distal symmetric polyneuropathy, history of stroke, systolic or diastolic blood pressure, average ankle:brachial index > 1.3 or non-compressible[27], or concentrations of white blood cell count, adiponectin, or IL-6. Longer duration of statin use was significantly and positively associated with age, BMI, T1D duration, and study-average LDLc concentration, and was significantly and negatively associated with insulin sensitivity (per estimated glucose disposal rate), and kidney function (estimated glomerular filtration rate). Increasing duration of statin use was associated with a lower prevalence of smoking and with a higher prevalence of coronary artery disease and proliferative retinopathy, of having a 14-year average A1c > 7.5% (> 58 mmol/mol), and of having a history of high blood pressure or using anti-hypertensive medication (Table 2, all $P < 0.05$).

A total of 30/108 (28%) participants met the study definition of cognitive impairment[18] and the percentage of participants with cognitive impairment increased with increasing duration of statin use: 14% of never users, 32% of 1-6 years of statin use, and 47% of 7-12 years of statin use (Table 2, $P = 0.003$). Longer duration of statin use was significantly related to worse performance on memory (Table 2, $P = 0.004$) and psychomotor speed (Table 2, $P = 0.012$), but no other domains (Table 2, all $P > 0.05$).

Cognitively impaired participants were significantly more likely to have coronary artery disease, a history of ever using statins, and for a longer duration, than

Table 2 Comparison of middle-aged adults with type 1 diabetes from the Pittsburgh Epidemiology of Diabetes Complications Study by duration of statin use

	Never used (*n* = 51)	1-6 yr (*n* = 25)	7-12 yr (*n* = 32)	*P* value[1]
Demographic and lifestyle factors, data are *n* (%), mean ± SD, or median (IQR)				
Age at cognitive testing (yr)	47.5 ± 7.3	51.8 ± 6.1	51.0 ± 6.7	0.02
Female	27 (53%)	16 (64%)	12 (38%)	0.10
Years of education	15 ± 2	16 ± 3	14 ± 3	0.52
Ever smoking 100+ cigarettes[5]	22 (43%)	11 (44%)	8 (25%)	0.05
Apo E4 (24, 34, 44)	16 (31%)	7 (28%)	11 (34%)	0.66
BMI (kg/m^2)	26.0 ± 4.3	27.6 ± 5.1	29.8 ± 4.7	0.002
Cognitive function				
Cognitively impaired	7 (14%)	8 (32%)	15 (47%)	0.003
Estimated verbal IQ	108.6 ± 8.2	107.7 ± 10.0	106.5 ± 6.9	0.24
Memory domain z-score	0.24 ± 0.75	-0.23 ± 0.64	-0.25 ± 0.78	0.004
Executive function z-score	0.18 ± 0.56	-0.10 ± 0.82	-0.30 ± 0.79	0.06
Psychomotor speed z-score	0.29 ± 0.66	-0.33 ± 1.10	-0.28 ± 0.89	0.01
Visuo-construction z-score	0.21 ± 0.64	-0.16 ± 0.82	-0.21 ± 1.45	0.13
Type 1 diabetes-related factors				
Diabetes duration (yr)	39.6 ± 5.8	43.4 ± 6.9	42.1 ± 6.5	0.03
Serum glucose (mg/dL)	188.6 ± 90.5	151.1 ± 73.6	173.0 ± 81.8	0.56
A1c > 7.5%, 14-yr average	27 (53%)	17 (68%)	25 (78%)	0.02
Glucose disposal rate (mg/kg per minutr)[2]	8.1 ± 2.0	7.5 ± 1.8	5.8 ± 2.9	< 0.001
Proliferative retinopathy[2]	17 (33%)	14 (58%)	20 (63%)	0.03
eGFR (mL/min per 1.73 m^2)[2,4]	91.3 ± 21.1	79.7 ± 20.1	74.7 ± 27.5	0.02
Coronary artery disease[2]	5 (10%)	3 (12%)	10 (31%)	0.02
Cardiac autonomic neuropathy[2]	21 (47%)	14 (58%)	13 (46%)	0.36
Distal symmetric polyneuropathy[2]	22 (49%)	13 (57%)	17 (53%)	0.61
Cardio-metabolic factors				
History of stroke[5]	1 (2%)	2 (8%)	2 (6%)	0.99
Systolic blood pressure (mmHg)	117.6 ± 12.0	119.6 ± 15.5	123.2 ± 19.3	0.44
Diastolic blood pressure (mmHg)	65.0 ± 9.5	64.6 ± 9.1	67.5 ± 10.6	0.18
History of high blood pressure[3]	13 (25%)	10 (40%)	16 (50%)	0.04
Study average LDLc (mg/dL)[5]	100.3 ± 25.6	112.2 ± 24.9	115.9 ± 24.7	0.02
Inflammatory markers				
[2]WBC × 10^3/mm^2	5.9 (5.0-6.7)	6.2 (5.2-6.9)	6.2 (5.2-7.1)	0.29
Adiponectin (μg/mL)[2]	22.0 (15.7-30.7)	21.8 (14.2-31.4)	22.3 (15.2-28.3)	0.75
IL-6 (ng/mL)[2]	1.4 (0.7-1.9)	1.2 (0.8-1.7)	1.2 (1.0-1.6)	0.28
TNFα (pg/mL)[2]	1.3 (1.0-2.3)	1.2 (1.0-1.8)	1.3 (1.0-1.6)	0.07
C-reactive protein (mg/L)[2]	0.9 (0.6-2.3)	0.9 (0.2-1.6)	1.9 (0.6-4.1)	0.08

[1]*P* values are adjusted for age and education; [2]Assessed in 2004-2006; [3]Defined as any EDC assessed SBP > 140 mmHg or DBP > 90, or ever self-reported use of anti-hypertensive medication from 1986-1988 through 2010-2013; [4]Estimated per the Chronic Kidney Disease - Epidemiology (CKD-EPI) formula; [5]Assessed from EDC baseline (1986-1988) through time of cognitive testing (2010-2013). Factors assessed at time of cognitive testing (2010-2013) unless otherwise specified. T1D: Type 1 diabetes; LDLc: Low density lipoprotein cholesterol; BMI: Body mass index; eGDR: Estimated glucose disposal rate; WBC: White blood cell count; IL-6: Interleukin-6; TNFα: Tumor necrosis factor alpha.

cognitively normal participants, independent of education (Table 3 all $P < 0.05$). While not statistically significant, cognitively impaired participants were more likely to have a higher study-average LDLc as compared with cognitively normal participants (Table 3, $P = 0.063$). Associations between cognitive impairment and history of high blood pressure/using anti-hypertensive medication and brain imaging data were not statistically significant (Table 3, all $P > 0.10$) (for details regarding relationships between other risk factors and cognitive impairment in this cohort, see references[18,28]).

In logistic regression models with cognitive impairment as the outcome, using statins for 1-6 years, as compared with never using statins, more than tripled the odds of cognitive impairment, but was only marginally significant after controlling for age and education (Table 4, Model 1). Compared with never using statins, statin use of 7-12 years was related to almost five-fold higher odds of cognitive impairment, independent of age or education (Table 4, Model 1). Controlling for long-term LDLc, coronary artery disease, or *Apo E4* allele status did not substantially alter the relationship between duration of statin use and cognitive impairment. Furthermore, LDLc, coronary artery disease, and *Apo E4* allele status were not significantly related to cognitive impairment (Table 4, Models 2-5). Results were overall unchanged when adjusting for white matter hyperintensities or left hippocampal volume (data not shown).

In linear regression models with memory domain z-score as the outcome, using statins for 1-6 years was related to half a SD decrease in memory domain score (Table 5, Model 1) as compared with never using statins. Using statins for 7-12 years was related to almost half a SD decrease in memory domain score (Table 5, Model 1) as compared with never using statins. Controlling for LDLc, coronary artery disease, or *Apo E4*

Table 3 Select characteristics[1] of middle-aged adults with childhood-onset type 1 diabetes from the Pittsburgh Epidemiology of Diabetes Complications Study, by cognitive impairment status

	Cognitively normal (*n* = 78)	Cognitively impaired (*n* = 30)	*P* value
Data are *n* (%), mean ± SD, or median (IQR)			
Coronary artery disease[2]	9 (12%)	9 (30%)	0.02
Cardio-metabolic risk factors			
Ever using statins (1986-2013)[3]	34 (44%)	23 (77%)	0.003
Duration of statin use (statin years)[3]	0 (0-6)	7 (2-8)	0.002
If statin use, only used lipophilic statin[3]	30 (88%)	21 (91%)	0.99
Study average LDLc (mg/dL)[3]	104.5 ± 25.8	115.9 ± 24.8	0.06
History of high blood pressure[4]	26 (33%)	13 (43%)	0.24
Brain imaging			
Severe White Matter Hyperintensities[5]	17 (26%)	11 (46%)	0.09
Left hippocampal volume[6]	0.31 ± 0.03	0.31 ± 0.03	0.31

Reported *P* value is adjusted for education. [1]Relationships between other factors and cognitive impairment in this type 1 diabetes cohort have been previously described and published elsewhere (for details, see Nunley *et al*[18], 2015); [2]Assessed in 2004-2006; [3]Assessed since EDC baseline (1986-1988) through time of cognitive testing (2010-2013); [4]Defined as any EDC assessed SBP > 140 mmHg or DBP > 90, or ever self-reported use of anti-hypertensive medication from 1986-1988 through 2010-2013; [5]Fazekas rating 2-3 *vs* Fazekas rating 1; data on *n* = 89 (for details, see Nunley *et al*[28], 2015); [6]Hippocampal volume as a percentage of total intracranial volume, data on *n* = 88 (for details, see Hughes *et al*[26], 2013). Measures assessed 2010-2013 unless otherwise noted. LDLc: Low density lipoprotein cholesterol.

Table 4 Results of logistic regression models assessing the association between duration of statin use and cognitive impairment in middle-aged adults with type 1 diabetes from the Pittsburgh Epidemiology of Diabetes Complications Study

	Variables in Model	Cognitive impairment OR (95%CI) *P* value
Model 1	Never used statins	Referent group
	1-6 yr statins	3.16 (0.93-10.72), *P* = 0.064
	7-12 yr statins	4.84 (1.63-14.44), *P* = 0.005
Model 2	Never used statins	Referent group
	1-6 yr statins	2.86 (0.83-9.86), *P* = 0.095
	7-12 yr statins	4.26 (1.40-13.00), *P* = 0.011
	Average LDLc	1.01 (0.99-1.03), *P* = 0.24
Model 3	Never used statins	Referent group
	1-6 yr statins	3.29 (0.95-11.40), *P* = 0.061
	7-12 yr statins	4.13 (1.35-12.60), *P* = 0.013
	CAD	2.88 (0.88-9.44), *P* = 0.081
Model 4	Never used statins	Referent group
	1-6 yr statins	3.14 (0.93-10.64), *P* = 0.066
	7-12 yr statins	4.95 (1.65-14.82), *P* = 0.004
	Apo E4 allele	0.73 (0.26-2.02), *P* = 0.55
Model 5	Never used statins	Referent group
	1-6 yr statins	2.90 (0.82-10.29), *P* = 0.099
	7-12 yr statins	3.69 (1.17-11.68), *P* = 0.026
	Average LDLc	1.01 (0.99-1.03), *P* = 0.24
	CAD	2.72 (0.81-9.13), *P* = 0.11
	Apo E4 allele	0.75 (0.26-2.15), *P* = 0.59

Statin use groups: Never used *n* = 51; 1-6 years *n* = 25; 7+ years *n* = 32. Binary outcome: Cognitive impairment present/absent. Model 1: Statin use groups, controlling for age and education; Model 2: Model 1, further controlling for average long-term LDLc (1986-1988 through 2010-2013); Model 3: Model 1, further controlling for prevalent coronary artery disease (CAD); Model 4: Model 1, further controlling for Apo E4 allele status (24, 34, or 44); Model 5: Model 1, further controlling for LDLc, CAD, and Apo E4 allele. LDLc: Low density lipoprotein cholesterol.

allele did not substantially alter the relationship between duration of statin use and lower memory domain score, and none of these factors were significantly related to memory domain score (Table 5, Models 2-5). Results were independent of brain imaging markers (data not shown).

Using propensity score analyses, those using statins for 1-6 years or for 7-12 years were three times more likely to have cognitive impairment as compared with never statin users; the association was borderline significant for those using statins 1-6 years (OR = 3.48, 95%CI: 0.97-12.51; *P* = 0.056) while the association was statistically significant for those using statins 7-12 years (OR = 3.62, 95%CI: 1.05-12.49; *P* = 0.042). Compared with never statin users, using statins for 1-6 years was statistically significantly related to worse memory z-score (Beta: -0.47, SE = 18, *P* = 0.012). While memory domain z-scores were lower for those using statins for 7-12 years than for never users, the difference did not reach statistical significance (Beta: -0.29, SE = 0.18; *P* = 0.12).

DISCUSSION

This study analyzed correlations between statin use and cognitive impairment in a sub-group of participants with T1D from the on-going, observational Pittsburgh Epidemiology of Diabetes Complications Study. These now middle-aged adults were diagnosed with T1D prior to age 18 years, and have reported medication use biennially since the parent study baseline in 1986. Among the 108 participants with a cognitive assessment in 2010-2013, using statins more than tripled the odds of having cognitive impairment discernible by middle age. As duration of statin use increased (never, 1-6 years, 7-12 years), an increasing percentage of participants met the study definition of cognitive impairment (14%, 32% and 47%, respectively), independent of age or education. Depressive symptoms were not associated with statin use, and we have previously shown depressive symptoms were not related to cognitive impairment in this cohort[28]. Results were robust to adjustment for prevalent coronary artery disease, *Apo E4* status, and long-term average LDL cholesterol concentration.

Our results contradict those reported by the only other study we know of to examine relationships between statin use and cognitive function in T1D cohort[17]. This could be due to several factors, including the small number of participants in the prior study who used statins (11 out of 55), the younger age of their participants (mean age 39 years), or that their study population included T1D cases diagnosed in adulthood (diabetes duration ranged from 6-35 years)[17], whereas our cases were all diagnosed in childhood. Furthermore,

Table 5 Results of linear regression models assessing the association between duration of statin use and memory domain function in middle-aged adults with type 1 diabetes from the Pittsburgh Epidemiology of Diabetes Complications Study

	Variables in Model	Memory domain standardized β, *P* value
Model 1	Never used statins	Referent group
	1-6 yr statins	-0.284, *P* = 0.003
	7-12 yr statins	-0.232, *P* = 0.01
Model 2	Never used statins	Referent group
	1-6 yr statins	-0.267, *P* = 0.006
	7-12 yr statins	-0.209, *P* = 0.031
	Average LDLc	-0.084, *P* = 0.34
Model 3	Never used statins	Referent group
	1-6 yr statins	-0.267, *P* = 0.006
	7-12 yr statins	-0.213, *P* = 0.032
	CAD	0.02, *P* = 0.86
Model 4	Never used statins	Referent group
	1-6 yr statins	-0.284, *P* = 0.003
	7-12 yr statins	-0.231, *P* = 0.014
	Apo E4 allele	-0.01, *P* = 0.92
Model 5	Never used statins	Referent group
	1-6 yr statins	-0.267, *P* = 0.007
	7-12 yr statins	-0.213, *P* = 0.034
	Average LDLc	-0.084, *P* = 0.35
	CAD	0.02, *P* = 0.86
	Apo E4 allele	-0.001, *P* = 0.99

Statin use groups: Never used n = 51; 1-6 years n = 25; 7-12 years n = 32. Outcome: Standardized score of seven tasks assessing memory domain (z-score, in SD units). Model 1: Statin use groups, controlling for age and education; Model 2: Model 1, further controlling for average long-term LDLc (1986-88 through 2010-2013); Model 3: Model 1, further controlling for prevalent coronary artery disease (CAD) as of 2004-2006; Model 4: Model 1, further controlling for *Apo E4* allele status (24, 34, or 44); Model 5: Model 1, further controlling for LDLc, CAD, and *Apo E4* allele. LDLc: Low density lipoprotein cholesterol.

the prior study did not provide information on duration of statin use in their T1D participants.

That statin use in our cohort was associated with poor performance of memory tasks is of particular interest for three reasons. First, memory problems are the most commonly reported cognitive complaint among statin users[29-32]. Second, with a mean age of 49 years, our T1D participants should not yet exhibit memory deficits commonly observed in adults ages 65 and older[33]. And third, our findings contradict prior reports that memory appears to be preserved in adult T1D populations[34-36]. Considering these three points, we believe additional studies are warranted to investigate the cognitive effects of statin use, along with other potential risk factors related to cognitive impairment and poor memory, in adults with childhood-onset T1D. Such studies should employ a longitudinal design, assessing cognitive performance repeatedly, with at least one done prior to initiating statin use, and with detailed ascertainments of statin use (*e.g.*, type, dose, age at initiation) over time. We believe this should be a public health priority given that the improved life expectancy of people with T1D[37] will lead to a rapidly-growing population of aging adults with T1D who are at risk of cognitive impairment, with high personal and societal costs.

While confounding by indication cannot be completely ruled out due to study design, we addressed this as best as possible in our statistical approach. Not only were relationships between statin use and cognitive outcomes independent of cardiovascular risk factors, they remained significant when controlling for coronary artery disease, long-term average LDL cholesterol concentration, *Apo E4* status, and two brain imaging measures known to affect cognitive performance. Furthermore, when incorporating the propensity score for statin use, statin use remained statistically significantly related to cognitive impairment, and to poor performance on memory tasks. Thus, based on our previous publication[18] and this study's results, we doubt that associations between statin use and poor cognitive outcomes are due merely to confounding by indication.

We examined statin class (lipophilic *vs* hydrophilic), a factor which may be an important consideration[31,38,39]. However, since almost all participants used lipophilic statins, analyses by statin class were not possible. Even though both classes of statins can cross the blood-brain barrier, lipophilic statins may accumulate in the brain more readily and/or rapidly than hydrophilic statins[39]. The exact nature of how statins affect the brain are unknown, and most of our knowledge is derived from animal or cell culture studies. Animal studies suggest that statins can exert negative impacts on both myelin[40-42] and neuronal health[2,3]. Other studies report neuroprotective effects of statins[43], while many studies show no effect (see reviews[6,44]). In addition, statins appear to promote cerebral angiogenesis at therapeutic doses, although angiostatic effects occur at higher concentrations[45].

Lastly, our study population differs from those of previous studies assessing statin use and cognitive function in two important ways: Our participants are middle-aged adults who were diagnosed with T1D in childhood, with a median duration of statin use of 6 years. This is in contrast to prior studies which primarily assessed relationships between statins and cognition in overall healthy, elderly adults aged 60 years and older, who used statins for only a short time; most previous cognitive studies examined statin use over periods of less than 3 wk to 1 year, although at least one study examined participants who used statins for 10+ years[5,6,46]. Moreover, these prior studies have not consistently shown evidence of a beneficial effect of statins on cognitive performance. In fact, the British Association for Psychopharmacology recently stated that "until further evidence is available, ...statins (among other drugs)… cannot be recommended either for the treatment or prevention of Alzheimer's disease"[47].

Why are these differences important? First, our participants have been exposed to metabolic dysregulation since childhood, a crucial period of brain development. This might make them more vulnerable to

negative consequences of statin therapy than would occur in people without T1D; if diabetes in childhood limited cerebral gray or white matter development, as brain imaging studies suggest, then these individuals may be less able to compensate for statin-related insults to the brain. Second, myelination occurs into early adulthood, with an additional "late wave" of myelination occurring during the 4th decade of life[48]. Exposure to statins during this time may negatively impact the myelination process, and these effects may be most noticeable in people with chronic diseases that negatively impact cerebral white matter development, as appears to occur in people with childhood-onset T1D[10]. Third, most prior studies were conducted in populations with much shorter exposure to statins than our participants have experienced. This is important because statins appear to promote glial progenitor cells to differentiate into oligodendrocytes, accompanied by a loss of uncommitted glial progenitor cells[16]. Thus, initiation of long-term statin use by middle-age, as is recommended for T1D patients, may reduce the pool of progenitor cells for future recruitment, thus making these patients less resilient to cerebral insults from normal aging or T1D-related vascular damage. This, in turn, may contribute to an increased risk for cognitive impairment in this vulnerable patient population.

These results, while compelling, need to be replicated before considering changes in how to best manage lipid profiles and cardiovascular risk in T1D. Limitations of the study include that study design does not allow us to test whether statin use preceded the onset of cognitive impairment. We cannot assess whether cessation of statin treatment would lead to improved cognitive function, particularly on memory tasks, because this is an observational study. Even though T1D duration was not related to cognitive impairment, these results may not be generalizable to middle-aged adults with adult-onset T1D, as such individuals are not exposed to diabetes-related metabolic disturbances during childhood, a critical window of brain development. Strengths of our study include a well-characterized T1D cohort with 25 years of risk factor data, use of an extensive neuropsychological test battery to assess multiple cognitive domains, and inclusion of brain imaging markers known to correlate with cognitive performance.

Identifying modifiable risk factors for cognitive impairment in T1D is an important public health concern because cognitive impairment may negatively impact these individuals' ability to adhere to their diabetes management regime, ultimately leading to higher healthcare costs, increased rates and/or severity of diabetes-related complications, disability, and quality of life issues. It is premature to make decisions about statin use in the management of cardiovascular risk in T1D based solely on the current study findings. At the same time, we encourage clinicians to engage their T1D patients in open dialog to address any concerns over perceived changes in cognitive function.

ACKNOWLEDGMENTS

We would like to thank the individuals with type 1 diabetes from the Pittsburgh Epidemiology of Diabetes Complications Study for their continued participation in this on-going study.

COMMENTS

Background

Type 1 diabetes (T1D) negatively affects cognitive function, but the risk factors contributing to cognitive impairment remain to be elucidated. This is particularly true for middle-aged and older adults living with diabetes since childhood and who are also experiencing the effects of advancing age on cognitive function.

Research frontiers

Statins are routinely prescribed for primary and secondary prevention of coronary events in people with T1D. Despite the on-going controversy regarding whether statins negatively impact cognitive function, especially the memory domain, there is a lack of data examining statins as a risk factor for cognitive impairment in this patient population.

Innovations and breakthroughs

As compared to never-statin users, statin use was related to greater odds of cognitive impairment. In addition, statin use was significantly related to lower performance on memory tasks. These relationships were robust to adjustment for coronary artery disease, long-term low density lipoprotein cholesterol levels, ApoE status, education, and age. Confounding by indication was also addressed using propensity score analysis.

Applications

Initiation of long-term statin use by middle-aged adults with childhood-onset T1D may negatively affect cognitive function, with strongest effects on memory. These results should be investigated in other T1D populations, preferentially in longitudinal studies with cognitive assessments and brain imaging assessed pre- and post- statin exposure.

Terminology

White matter hyperintensities are non-specific brain imaging markers of cerebral small vessel disease and are highly correlated to cognitive impairment and depression in adults ages 65 and older. Different visual rating scales are used to classify their severity; the authors chose the Fazekas scale, with "1" indicating mild white matter hyperintensities, and "2" or "3" indicating moderate to severe white matter hyperintensities.

Peer-review

This paper aims to test the correlation between statin use and cognitive impairment in adults with childhood-onset T1D, as a group of patients with chronic exposure to metabolic dysregulation. It is a valuable study, and the results are well analyzed.

REFERENCES

1 **Goldstein MR**, Mascitelli L. Regarding long-term statin therapy: are we trading stronger hearts for weaker brains? *Med Hypotheses* 2014; **83**: 346-351 [PMID: 24986644 DOI: 10.1016/j.mehy.2014.06.010]

2 **März P**, Otten U, Miserez AR. Statins induce differentiation and cell death in neurons and astroglia. *Glia* 2007; **55**: 1-12 [PMID: 16998865 DOI: 10.1002/glia.20422]

3 **Schulz JG**, Bösel J, Stoeckel M, Megow D, Dirnagl U, Endres M. HMG-CoA reductase inhibition causes neurite loss by interfering with geranylgeranylpyrophosphate synthesis. *J Neurochem* 2004; **89**: 24-32 [PMID: 15030386 DOI: 10.1046/j.1471-4159.2003.02305.x]

4 **Chatterjee S**, Krishnamoorthy P, Ranjan P, Roy A, Chakraborty A, Sabharwal MS, Ro R, Agarwal V, Sardar P, Danik J, Giri JS, DeGoma EM, Kumbhani DJ. Statins and cognitive function: an updated review. *Curr Cardiol Rep* 2015; **17**: 4 [PMID: 25618304 DOI: 10.1007/s11886-014-0559-3]

5 **Ott BR**, Daiello LA, Dahabreh IJ, Springate BA, Bixby K, Murali M, Trikalinos TA. Do statins impair cognition? A systematic review and meta-analysis of randomized controlled trials. *J Gen Intern Med* 2015; **30**: 348-358 [PMID: 25575908 DOI: 10.1007/s11606-014-3115-3]

6 **Power MC**, Weuve J, Sharrett AR, Blacker D, Gottesman RF. Statins, cognition, and dementia—systematic review and methodological commentary. *Nat Rev Neurol* 2015; **11**: 220-229 [PMID: 25799928 DOI: 10.1038/nrneurol.2015.35]

7 **Richardson K**, Schoen M, French B, Umscheid CA, Mitchell MD, Arnold SE, Heidenreich PA, Rader DJ, deGoma EM. Statins and cognitive function: a systematic review. *Ann Intern Med* 2013; **159**: 688-697 [PMID: 24247674 DOI: 10.7326/0003-4819-159-10-201311190-00007]

8 **Biessels GJ**, Reijmer YD. Brain changes underlying cognitive dysfunction in diabetes: what can we learn from MRI? *Diabetes* 2014; **63**: 2244-2252 [PMID: 24931032 DOI: 10.2337/db14-0348]

9 **Koekkoek PS**, Kappelle LJ, van den Berg E, Rutten GE, Biessels GJ. Cognitive function in patients with diabetes mellitus: guidance for daily care. *Lancet Neurol* 2015; **14**: 329-340 [PMID: 25728442 DOI: 10.1016/S1474-4422(14)70249-2]

10 **Mauras N**, Mazaika P, Buckingham B, Weinzimer S, White NH, Tsalikian E, Hershey T, Cato A, Cheng P, Kollman C, Beck RW, Ruedy K, Aye T, Fox L, Arbelaez AM, Wilson D, Tansey M, Tamborlane W, Peng D, Marzelli M, Winer KK, Reiss AL. Longitudinal assessment of neuroanatomical and cognitive differences in young children with type 1 diabetes: association with hyperglycemia. *Diabetes* 2015; **64**: 1770-1779 [PMID: 25488901 DOI: 10.2337/db14-1445]

11 **American Diabetes Association.** Standards of Medical Care in Diabetes-2016 Abridged for Primary Care Providers. *Clin Diabetes* 2016; **34**: 3-21 [PMID: 26807004 DOI: 10.2337/diaclin.34.1.3]

12 **Belay B**, Belamarich PF, Tom-Revzon C. The use of statins in pediatrics: knowledge base, limitations, and future directions. *Pediatrics* 2007; **119**: 370-380 [PMID: 17272627 DOI: 10.1542/peds.2006-0787]

13 **van der Vaart T**, Plasschaert E, Rietman AB, Renard M, Oostenbrink R, Vogels A, de Wit MC, Descheemaeker MJ, Vergouwe Y, Catsman-Berrevoets CE, Legius E, Elgersma Y, Moll HA. Simvastatin for cognitive deficits and behavioural problems in patients with neurofibromatosis type 1 (NF1-SIMCODA): a randomised, placebo-controlled trial. *Lancet Neurol* 2013; **12**: 1076-1083 [PMID: 24090588 DOI: 10.1016/S1474-4422(13)70227-8]

14 **Salat DH**, Tuch DS, Hevelone ND, Fischl B, Corkin S, Rosas HD, Dale AM. Age-related changes in prefrontal white matter measured by diffusion tensor imaging. *Ann N Y Acad Sci* 2005; **1064**: 37-49 [PMID: 16394146 DOI: 10.1196/annals.1340.009]

15 **Courchesne E**, Chisum HJ, Townsend J, Cowles A, Covington J, Egaas B, Harwood M, Hinds S, Press GA. Normal brain development and aging: quantitative analysis at in vivo MR imaging in healthy volunteers. *Radiology* 2000; **216**: 672-682 [PMID: 10966694 DOI: 10.1148/radiology.216.3.r00au37672]

16 **Sim FJ**, Lang JK, Ali TA, Roy NS, Vates GE, Pilcher WH, Goldman SA. Statin treatment of adult human glial progenitors induces PPAR gamma-mediated oligodendrocytic differentiation. *Glia* 2008; **56**: 954-962 [PMID: 18383345 DOI: 10.1002/glia.20669]

17 **Moryś JM**, Kozera GM, Neubauer-Geryk J, Kruszewski P, Wolnik B, Nyka WM, Bieniaszewski L. Statin Use and Cognitive Impairment in Patients With Type 1 Diabetes: An Observational Study. *Clin Neuropharmacol* 2016; **39**: 182-187 [PMID: 27046662 DOI: 10.1097/wnf.0000000000000158]

18 **Nunley KA**, Rosano C, Ryan CM, Jennings JR, Aizenstein HJ, Zgibor JC, Costacou T, Boudreau RM, Miller R, Orchard TJ, Saxton JA. Clinically Relevant Cognitive Impairment in Middle-Aged Adults With Childhood-Onset Type 1 Diabetes. *Diabetes Care* 2015; **38**: 1768-1776 [PMID: 26153270 DOI: 10.2337/dc15-0041]

19 **Ardila A**. Normal aging increases cognitive heterogeneity: analysis of dispersion in WAIS-III scores across age. *Arch Clin Neuropsychol* 2007; **22**: 1003-1011 [PMID: 17904332 DOI: 10.1016/j.acn.2007.08.004]

20 **Dore GA**, Elias MF, Robbins MA, Elias PK, Brennan SL. Cognitive performance and age: norms from the Maine-Syracuse Study. *Exp Aging Res* 2007; **33**: 205-271 [PMID: 17497370 DOI: 10.1080/03610730701319087]

21 **Strauss E**, Sherman EMS, Spreen O. A compendium of neuropsychological tests: administrations, norms and commentary, 3rd Ed. New York: Oxford University Press, 2006: 1-1216

22 **Saxton J**, Snitz BE, Lopez OL, Ives DG, Dunn LO, Fitzpatrick A, Carlson MC, Dekosky ST. Functional and cognitive criteria produce different rates of mild cognitive impairment and conversion to dementia. *J Neurol Neurosurg Psychiatry* 2009; **80**: 737-743 [PMID: 19279031 DOI: 10.1136/jnnp.2008.160705]

23 **Beck AT**, Steer RA, Carbin, MG. Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clin Psychol Rev* 1988; **8**: 77-100 [DOI: 10.1016/0272-7358(88)90050-5]

24 **Pambianco G**, Costacou T, Ellis D, Becker DJ, Klein R, Orchard TJ. The 30-year natural history of type 1 diabetes complications: the Pittsburgh Epidemiology of Diabetes Complications Study experience. *Diabetes* 2006; **55**: 1463-1469 [PMID: 16644706 DOI: 10.2337/db05-1423]

25 **Nunley KA**, Ryan CM, Orchard TJ, Aizenstein HJ, Jennings JR, Ryan J, Zgibor JC, Boudreau RM, Costacou T, Maynard JD, Miller RG, Rosano C. White matter hyperintensities in middle-aged adults with childhood-onset type 1 diabetes. *Neurology* 2015; **84**: 2062-2069 [PMID: 25904692 DOI: 10.1212/WNL.0000000000001582]

26 **Hughes TM**, Ryan CM, Aizenstein HJ, Nunley K, Gianaros PJ, Miller R, Costacou T, Strotmeyer ES, Orchard TJ, Rosano C. Frontal gray matter atrophy in middle aged adults with type 1 diabetes is independent of cardiovascular risk factors and diabetes complications. *J Diabetes Complications* 2013; **27**: 558-564 [PMID: 23994432 DOI: 10.1016/j.jdiacomp.2013.07.001]

27 **Ix JH**, Miller RG, Criqui MH, Orchard TJ. Test characteristics of the ankle-brachial index and ankle-brachial difference for medial arterial calcification on X-ray in type 1 diabetes. *J Vasc Surg* 2012; **56**: 721-727 [PMID: 22560306 DOI: 10.1016/j.jvs.2012.02.042]

28 **Nunley KA**, Ryan CM, Saxton JA, Costacou T, Orchard TJ, Rosano C. Response to Comment on Nunley et al. Clinically Relevant Cognitive Impairment in Middle-Aged Adults With Childhood-Onset Type 1 Diabetes. Diabetes Care 2015; 38: 1768-1776. *Diabetes Care* 2016; **39**: e25 [PMID: 26798154 DOI: 10.2337/dci15-0028]

29 **Padala KP**, Padala PR, McNeilly DP, Geske JA, Sullivan DH, Potter JF. The effect of HMG-CoA reductase inhibitors on cognition in patients with Alzheimer's dementia: a prospective withdrawal and rechallenge pilot study. *Am J Geriatr Pharmacother* 2012; **10**: 296-302 [PMID: 22921881 DOI: 10.1016/j.amjopharm.2012.08.002]

30 **Strom BL**, Schinnar R, Karlawish J, Hennessy S, Teal V, Bilker WB. Statin Therapy and Risk of Acute Memory Impairment. *JAMA Intern Med* 2015; **175**: 1399-1405 [PMID: 26054031 DOI: 10.1001/jamainternmed.2015.2092]

31 **Evans MA**, Golomb BA. Statin-associated adverse cognitive effects: survey results from 171 patients. *Pharmacotherapy* 2009; **29**: 800-811 [PMID: 19558254 DOI: 10.1592/phco.29.7.800]

32 **Rojas-Fernandez CH**, Cameron JC. Is statin-associated cognitive impairment clinically relevant? A narrative review and clinical recommendations. *Ann Pharmacother* 2012; **46**: 549-557 [PMID: 22474137 DOI: 10.1345/aph.1Q620]

33 **Koen JD**, Yonelinas AP. The effects of healthy aging, amnestic mild cognitive impairment, and Alzheimer's disease on recollection and familiarity: a meta-analytic review. *Neuropsychol Rev* 2014; **24**: 332-354 [PMID: 25119304 DOI: 10.1007/s11065-014-9266-5]

34 **McCrimmon RJ**, Ryan CM, Frier BM. Diabetes and cognitive dysfunction. *Lancet* 2012; **379**: 2291-2299 [PMID: 22683129 DOI: 10.1016/S0140-6736(12)60360-2]

35 **Brands AM**, Biessels GJ, de Haan EH, Kappelle LJ, Kessels RP. The effects of type 1 diabetes on cognitive performance: a meta-

analysis. *Diabetes Care* 2005; **28**: 726-735 [PMID: 15735218 DOI: 10.2337/diacare.28.3.726]
36 **Brands AMA**, Kessels, RPC, Ryan, CM. Cognition in adults with type 1 diabetes. In: Biessels GJ, Luchsinger JA. Contemporary Diabetes: Diabetes and the Brain. New York: Humana Press of Springer Science Business Media LLC, 2009: 277-293
37 **Miller RG**, Secrest AM, Sharma RK, Songer TJ, Orchard TJ. Improvements in the life expectancy of type 1 diabetes: the Pittsburgh Epidemiology of Diabetes Complications study cohort. *Diabetes* 2012; **61**: 2987-2992 [PMID: 22851572 DOI: 10.2337/db11-1625]
38 **Glasser SP**, Wadley V, Judd S, Kana B, Prince V, Jenny N, Kissela B, Safford M, Prineas R, Howard G. The association of statin use and statin type and cognitive performance: analysis of the reasons for geographic and racial differences in stroke (REGARDS) study. *Clin Cardiol* 2010; **33**: 280-288 [PMID: 20513066 DOI: 10.1002/clc.20758]
39 **McFarland AJ**, Anoopkumar-Dukie S, Arora DS, Grant GD, McDermott CM, Perkins AV, Davey AK. Molecular mechanisms underlying the effects of statins in the central nervous system. *Int J Mol Sci* 2014; **15**: 20607-20637 [PMID: 25391045 DOI: 10.3390/ijms151120607]
40 **Miron VE**, Zehntner SP, Kuhlmann T, Ludwin SK, Owens T, Kennedy TE, Bedell BJ, Antel JP. Statin therapy inhibits remyelination in the central nervous system. *Am J Pathol* 2009; **174**: 1880-1890 [PMID: 19349355 DOI: 10.2353/ajpath.2009.080947]
41 **Xiang Z**, Reeves SA. Simvastatin induces cell death in a mouse cerebellar slice culture (CSC) model of developmental myelination. *Exp Neurol* 2009; **215**: 41-47 [PMID: 18929563 DOI: 10.1016/j.expneurol.2008.09.010]
42 **Klopfleisch S**, Merkler D, Schmitz M, Klöppner S, Schedensack M, Jeserich G, Althaus HH, Brück W. Negative impact of statins on oligodendrocytes and myelin formation in vitro and in vivo. *J Neurosci* 2008; **28**: 13609-13614 [PMID: 19074034 DOI: 10.1523/jneurosci.2765-08.2008]
43 **Paintlia AS**, Paintlia MK, Singh I, Skoff RB, Singh AK. Combination therapy of lovastatin and rolipram provides neuroprotection and promotes neurorepair in inflammatory demyelination model of multiple sclerosis. *Glia* 2009; **57**: 182-193 [PMID: 18720408 DOI: 10.1002/glia.20745]
44 **Butterfield DA**, Barone E, Mancuso C. Cholesterol-independent neuroprotective and neurotoxic activities of statins: perspectives for statin use in Alzheimer disease and other age-related neurodegenerative disorders. *Pharmacol Res* 2011; **64**: 180-186 [PMID: 21536132 DOI: 10.1016/j.phrs.2011.04.007]
45 **Weis M**, Heeschen C, Glassford AJ, Cooke JP. Statins have biphasic effects on angiogenesis. *Circulation* 2002; **105**: 739-745 [PMID: 11839631 DOI: 10.1161/hc0602.103393]
46 **Macedo AF**, Taylor FC, Casas JP, Adler A, Prieto-Merino D, Ebrahim S. Unintended effects of statins from observational studies in the general population: systematic review and meta-analysis. *BMC Med* 2014; **12**: 51 [PMID: 24655568 DOI: 10.1186/1741-7015-12-51]
47 **O'Brien JT**, Holmes C, Jones M, Jones R, Livingston G, McKeith I, Mittler P, Passmore P, Ritchie C, Robinson L, Sampson EL, Taylor JP, Thomas A, Burns A. Clinical practice with anti-dementia drugs: A revised (third) consensus statement from the British Association for Psychopharmacology. *J Psychopharmacol* 2017; **31**: 147-168 [PMID: 28103749 DOI: 10.1177/0269881116680924]
48 **Lebel C**, Gee M, Camicioli R, Wieler M, Martin W, Beaulieu C. Diffusion tensor imaging of white matter tract evolution over the lifespan. *Neuroimage* 2012; **60**: 340-352 [PMID: 22178809 DOI: 10.1016/j.neuroimage.2011.11.094]

P- Reviewer: Navedo MF, Papaccio G, Sanlioglu AD, Zhang Q
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Wu HL

Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com