Journal of the Neurological Sciences 403 (2019) 133–138

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Late life insulin resistance and Alzheimer's disease and dementia: The Kuakini Honolulu heart program

Thomas H. Lee[a,*], Eric L. Hurwitz[a], Robert V. Cooney[a], Yan Yan Wu[a], Chen-Yen Wang[b], Kamal Masaki[c,d], Andrew Grandinetti[a]

[a] Office of Public Health Studies, University of Hawai'i at Mānoa, Honolulu, HI, United States of America
[b] School of Nursing and Dental Hygiene, University of Hawai'i at Mānoa, Honolulu, HI, United States of America
[c] Department of Geriatric Medicine, John A. Burns School of Medicine, University of Hawai'i at Mānoa, Honolulu, HI, United States of America
[d] Kuakini Medical Center, Honolulu, HI, United States of America

ARTICLE INFO

Keywords:
Insulin resistance
Alzheimer's disease
Dementia
Aging

ABSTRACT

Introduction: Recent findings outline negative effects of brain insulin signaling on memory due to hyperinsulinemia. We investigated the association between insulin resistance (IR) with AD and dementia.
Methods: Later life Japanese men ($N = 1544$, mean age = 79.9 years) with normal cognitive function were followed from exam 4 to 5 of the Kuakini Honolulu Asia Aging Study. Subjects underwent physical exams, blood draws, and neuropsychological testing. IR status was determined at exam 4 using the McAuley and HOMA indices. Subjects with prevalent diabetes and dementia were excluded. Incident dementia and AD cases were determined at exam 5.
Results: IR was associated with decreased odds of AD and dementia using both IR indices. Carriers of the *APOE* ε4 allele had 15% increased odds of AD and dementia.
Discussion: Our findings provide insight regarding possible inverse relationship between IR and AD in elderly Japanese men, and support biologic studies showing short term hyperinsulinemia improves memory and cognitive function.

1. Introduction

According to a 2013 report on world population prepared by the United Nation's Population Division, the population of persons aged 60 years and older will triple from 841 million in 2013, to over two billion by 2050 [1]. Alzheimer's disease is one of the leading neurologic diseases diagnosed in older adults and is the most common form of dementia [2]. Projected prevalence of worldwide AD ranges from 84 million by 2040 to over 100 million by 2050 [3,4]. Type 2 Diabetes (T2D) has been shown to increase the risk of dementia as well as AD [5–8], even to the point that AD was considered Type 3 diabetes [9].

The mechanisms through which T2D may increase the risk of dementia and AD are still up for debate. Insulin's role in neuronal signaling is the target of recent investigation. Insulin receptors (IRec) and insulin growth factors (IGFs) are found in large numbers in parts of the brain responsible for memory, such as the hippocampus, hypothalamus, and cerebral cortex [10,11]. Insulin signaling is responsible for neuronal survival, memory formation, memory retrieval, synaptic plasticity and learning [12].

It is widely known that insulin resistance (IR) is a precursor to T2D [13]. Although current research focuses on finding relationships between AD and T2D, very few studies exist that look at IR and AD or dementia. Two longitudinal studies found that midlife IR was associated with a small increased risk of AD [14,15]. The relationship between later life IR and AD has not yet been examined. The Kuakini Honolulu-Asia Aging Study (HAAS) allows for examination of the association of later life IR and AD.

2. Methods

2.1. Study population

The Kuakini Honolulu Heart Program (HHP) is a longitudinal study funded by the National Heart, Lung, and Blood Institute that focused on heart disease and stroke in a cohort of 8006 Japanese-American men born between 1900 and 1919, who were living on Oahu at the time of the baseline examination in 1965. Participants were identified using World War II selective service records. Details of the study have been

* Corresponding author at: University of Hawai'i at Mānoa, Office of Public Health Studies, 1960 East-West Road, Honolulu, HI 96822, United States of America.
E-mail address: Tlee3@hawaii.edu (T.H. Lee).

https://doi.org/10.1016/j.jns.2019.06.031
Received 5 February 2019; Received in revised form 3 June 2019; Accepted 27 June 2019
Available online 28 June 2019

described elsewhere [16].

In 1991, the Kuakini Honolulu-Asia Aging Study (HAAS) was established to begin research on risk factors associated with aging and neurodegenerative disorders. Baseline dementia status was established at the fourth examination (prevalent phase) on 3734 surviving individuals. Prevalent dementia cases (n = 226) and other missing CASI data (n = 111) were excluded. Subjects with other missing data at the fourth examination (n = 452), who were diagnosed as prevalent type 2 diabetic cases (n = 596), or who did not respond or died before 3-year follow-up (n = 916) were also excluded from this analysis. A total of 1544 subjects with complete information were used for this study. Incident dementia and incident AD cases were identified at the fifth examination, three years following the baseline Kuakini HAAS examination.

The Institutional Review Board (IRB) of the University of Hawaii at Manoa and the IRB of Kuakini Medical Center approved the study.

2.2. Diagnosis of dementia and AD

The 100 point Cognitive Abilities Screening Instrument [17] was administered to all subjects in the fourth examination and all subsequent examinations to screen for dementia cases [18]. The CASI is a well-recognized instrument and has been validated among Western and Japanese sample populations [19]. In exam four, CASI score and age determined a subgroup of participants for further dementia evaluation using stratified random sampling. During the fifth examination, an education-adjusted cutoff (79 for those with high education and 77 for those with low education) or an absolute drop of ≥9 points were applied to identify subjects to undergo further dementia examination [20]. Participants requiring further dementia diagnosis underwent clinical assessments that included detailed neuropsychological assessment and a proxy interview, and those diagnosed with dementia underwent blood tests and neuroimaging. A consensus committee consisting of the study's neurologist and at least two other physicians with expertise in geriatric medicine and dementia were responsible for the final diagnosis of dementia.

Dementia was diagnosed using the DSM-III/R criteria [21]. Criteria from the National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association were used to diagnose all possible and probable AD cases [22]. For the analysis, dementia was grouped as total dementia (included all causes of dementia); and AD, with CVD or without CVD. Based on established neuropathological criteria [23], 65% of clinical AD cases met the criteria for definite or probable AD [24].

2.3. Assessment of insulin resistance

Insulin resistance was estimated using the Homeostatic Model Assessment (HOMA) and the McAuley index. HOMA-IR index was calculated as fasting insulin (μU/mL) × fasting blood glucose (mg/dL)/405 [25]. McAuley Index was calculated as exp.[2.63–0.28 * ln fasting insulin (μU/ml)-0.31 * ln fasting triglycerides (mmol/l)] [26]. The Japan Diabetes Society recommended HOMA values ≥2.5 as identifying IR and this cutoff has been used in previous Asian Studies, and a cut off of ≤5.8 based off the McAuley index were considered IR [26,27].

2.4. Measure of confounders and mediators

APOE ε4 allele has been shown to be an effect modifier in the relationship between IR and dementia and AD in Japanese cohorts [15,28]. APOE ε4 allele genotyping was performed using PCR amplification, following the method of Hixson and Vernier [29]. Participants with at least one copy of the ε4 allele were categorized as APOE ε4 allele positive. Those with genotype ε2ε4 were excluded from the analysis due to possible opposing effect of ε2 and ε4 alleles on dementia [30].

Later life age, hypertension [31–33], BMI [34–36], smoking [37,38], alcohol consumption [39] and change in total cholesterol [40] are possible confounders in this study. In addition to BMI, waist circumference (WC) was also used as a more accurate measure of visceral adiposity [41].Prevalent hypertension was defined as systolic blood pressure ≥ 140 mm HG, diastolic blood pressure ≥ 90 mm HG or use of hypertensive medication [42]. Smoking status at exam 2 was self-reported and categorized by never, past, or current smoker. Alcohol was measured in ounces per month consumed, then recoded into non drinker, < 1 drink a day (up to 3 oz per month), 1–2 drinks per day (3 to 30 oz per month) and ≥3 drinks per day. An Autoanalyzer 1 N24B cholesterol method was used to determine total cholesterol values [16]. Stewart et al. [40] found that a decrease in total serum cholesterol from midlife to later life is associated with dementia and AD. Therefore, change in total cholesterol is represented by the difference between Exam 4 and Exam 1 total cholesterol values. BMI (kg/m^2) at exam 4 was calculated from participant's height and weight. Waist circumference at exam 4 was measured in cm.

2.5. Statistical analysis

Statistical analysis was conducted using SAS software version 9 (SAS Institute, Cary, NC). Univariate and bivariate analysis included comparing cohort characteristics between AD status, dementia status and IR status using Pearson Chi Square test or *t*-test as deemed appropriate. To account for the non-normal distribution of HOMA, HOMA was recoded into quartiles. Incident dementia and AD cases from exam 5 and exam 6 were included for this analysis. Because time at risk was not calculated, odds ratios for dementia and AD associated with later life IR were estimated by logistic regression. Dementia and AD are considered rare diseases, therefore the odds ratios were used to estimate the risk of disease by IR status. Logistic regression analyses were performed as crude and adjusted for possible confounders.

In addition to the unadjusted model, three adjusted models were examined: the first model included age, BMI, alcohol, change in total cholesterol and smoking; the second model included variables form model one and prevalent hypertension; the third model utilized WC instead of BMI.

3. Results

The baseline characteristics of study population are shown in Tables 1 and 2.

Of the 1544 subjects with complete information at baseline, a total of 132 developed dementia, of which 80 was AD. Subjects divided by HOMA status significantly differed by age, BMI and prevalent hypertension status. Differences between McAuley index status reflected those found using HOMA. Additionally, smoking status, and incident dementia status and incident AD also differed by McAuley and Combined indices. Subjects who were diagnosed with dementia were significantly older and had lower BMI; differed by IR using the McAuley and Combined indices. AD subjects were significantly older than non-AD subjects, and also differed by their IR status (McAuley and Combined indices).

In unadjusted logistic regression models, IR subjects had decreased odds of dementia by both the McAuley index (OR 0.53 95%CI 0.35–0.80) and the Combined index (OR 0.58 95%CI 0.38–0.87) (Table 3). Subjects who were IR by both McAuley and Combined indices saw a significant reduction in odds of incident AD [43].

After adjusting for potential confounders, including prevalent hypertension, the observed inverse association for dementia remained statistically significant for subjects who were IR by the McAuley index (Table 3). In the final adjusted models, regardless of IR index, subjects who were older had at least a 15% increased odds for dementia and AD. Subjects with the APOE ε4 allele had an increased odds of dementia (OR

Table 1
Selected characteristics of Participants by Insulin Resistance status determined by HOMA index, McAuley index, and the Combined index: The Kuakini Honolulu-Asia Aging Study.

Variables		HOMA			McAuley			Combined		
		Yes	No	P-Value	Yes	No	P-Value	Yes	No	P-Value
N = 1544		950 (61.5%)	594 (38.5%)	N/A	578 (37.4%)	966 (62.6%)	N/A	550 (35.6%)4	994 (65.4%)	N/A
Age (years)		76.8 ± 3.7	77.4 ± 3.9	0.001	76.6 ± 3.6	77.2 ± 3.9	0.001	76.6 ± 3.6	77.2 ± 3.9	0.006
APOE ε4	Yes	169 (17.8%)	105 (17.7%)	0.96	112 (19.4%)	162 (16.8%)	0.19	109 (19.8%)	165 (16.6%)	0.11
BMI at Exam 4		24.5 ± 2.8	22.0 ± 2.6	< 0.0001	25.0 ± 2.8	22.8 ± 2.8	< 0.0001	25.1 ± 2.8	22.8 ± 2.8	< 0.0001
Waist circumference at Exam 4		88.5 ± 7.8	81.7 ± 7.3	< 0.0001	89.9 ± 7.6	83.5 ± 7.8	< 0.0001	90.1 ± 7.6	83.6 ± 7.8	< 0.0001
Prevalent Hypertension	Yes	722 (76.0%)	384 (64.7%)	< 0.0001	453 (78.4%)	653 (67.6%)	< 0.0001	432 (78.6%)	672 (67.8%)	< 0.0001
Prevalent CHD	Yes	166 (17.5%)	89 (15.0%)	0.20	107 (18.5%)	148 (15.3%)	0.10	106 (19.3%)	149 (15.0%)	0.03
Change in total cholesterol		24.3 ± 35.1	23.3 ± 36.0	0.58	24.2 ± 36.5	23.8 ± 34.8	0.86	24.2 ± 36.2	23.8 ± 35.0	0.83
Smoking	Current	307 (32.3%)	173 (29.1%)	0.21	210 (36.3%)	270 (28.0%)	0.001	203 (36.9%)	277 (27.9%)	0.001
	Past	305 (32.1%)	186 (31.3%)		179 (31.0%)	312 (32.3%)		166 (30.2%)	325 (32.7%)	
	Never	338 (35.6%)	235 (39.6%)		189 (32.7%)	384 (39.7%)		181 (32.9%)	392 (39.4%)	
Alcohol (Exam 4)	≥3 a day	159 (16.7%)	103 (17.3%)	0.37	96 (16.6%)	166 (17.2%)	0.82	90 (17.4%)	172 (17.3%)	0.73
	1 to 2 a day	298 (31.4%)	209 (35.2%)		186 (32.2%)	321 (33.2%)		176 (32.0%)	331 (33.2%)	
	< 1 a day	90 (9.5%)	52 (8.8%)		58 (10.0%)	84 (8.7%)		56 (10.2%)	86 (8.7%)	
	Non-Drinker	403 (42.4%)	230 (38.7%)		238 (41.2%)	395 (40.9%)		228 (41.4%)	405 (40.8%)	
Incident dementia	Yes	71 (7.5%)	61 (10.3%)	0.06	33 (5.7%)	99 (10.3%)	0.002	33 (6.0%)	99 (10.0%)	0.008
Incident AD	Yes	42 (4.4%)	38 (6.4%)	0.09	20 (3.5%)	60 (6.2%)	0.02	20 (3.6%)	60 (6.0%)	0.04

1.21 95%CI 0.78–1.89) and AD (OR 1.07 95%CI 0.60–1.90).

The inverse relationship between IR and incident dementia remained after stratification by presence of the APOE ε4 allele, hypertension, or CHD (Table 4). Additionally, stratification by those same variables did not change the relationship between IR and incident AD, except when stratifying by CHD. Among subjects with CHD, those who were IR had increased odds of AD. However, the OR estimates for Table 5 are not statistically significant due to the small number of cases within the strata.

4. Discussion

This is the first study that looks at possibility of later-life IR as a risk factor for incident AD and dementia, using two distinct insulin resistance indices. Our data shows an inverse relationship between IR and AD, using either of the two IR indices. These results conflict with a previous study in the Kuakini HAAS that looked at fasting insulin and incident dementia where a U shaped distribution of dementia cases by fasting insulin level was reported [44]. However, subjects with extreme levels of fasting insulin were included in that study, which may have contributed to the right side of their U shaped curve. Consequently, all subjects with extreme fasting insulin levels were eliminated from our study cohort. Our findings did not show any non-linear association between IR and incident AD or incident dementia.

Studies investigating the association between IR and AD are less common. A cross-sectional study conducted in Hisayama, Japan found that IR subjects had a 64% increased odds of having neuritic plaques [45] while another cross-sectional study showed greater odds of AD in subjects with higher fasting insulin levels [46]. Three longitudinal studies looking at IR and AD had mixed results. Subjects with IR in the Rotterdam Study had a higher risk of AD up to three years after baseline. However, that association no longer remained in subsequent examinations after 3 years [14]. The Uppsala Longitudinal Study of Adult Men found that IR was associated with AD only in subjects with the APOE ε4 allele [15]. The Baltimore Longitudinal Study of Aging utilized autopsies to identify AD cases and no association was found between HOMA and AD [47].

Our findings of an inverse relationship between IR and AD may be explained by a couple of theories. It is widely accepted that the brain houses many IRec and IGF. Brain insulin signaling results in autophosphorylation of the IRec and triggers downstream tyrosine kinase pathways which have been shown to affect synaptic plasticity [11].

Table 2
Selected characteristics of Participants by incident Alzheimer's disease and dementia status: The Kuakini Honolulu-Asia Aging Study.

Variables		Dementia			Alzheimer's disease		
		Yes	No	P-Value	Yes	No	P-Value
N = 1544		132 (8.5%)	1412 (91.5%)	N/A	80 (5.2%)	1464 (94.8%)	N/A
Age (years)		79.3 ± 4.3	76.8 ± 3.7	< 0.0001	79.5 ± 4.4	76.9 ± 3.7	< 0.0001
APOE ε4	Yes	27 (20.5%)	247 (17.5%)	0.39	15 (18.8%)	259 (17.7%)	0.80
BMI at Exam 4		22.9 ± 3.1	23.7 ± 3.0	0.001	23.0 ± 2.9	23.6 ± 3.0	0.05
Waist circumference at Exam 4		84.4 ± 8.6	86.1 ± 8.3	0.025	84.6 ± 8.9	86.0 ± 8.3	0.14
Prevalent hypertension	Yes	103 (78.0%)	1003 (71.0%)	0.08	59 (73.8%)	1047 (71.5%)	0.67
Prevalent CHD	Yes	22 (16.7%)	233 (16.5%)	0.20	10 (12.5%)	245 (16.7%)	0.32
Change in total cholesterol		26.4 ± 33.0	23.7 ± 35.6	0.41	23.4 ± 33.4	24.0 ± 35.5	0.89
Smoking	Current	34 (25.8%)	446 (31.6%)	0.15	21 (26.3%)	459 (31.4%)	0.32
	Past	39 (29.5%)	452 (32.0%)		23 (28.7%)	468 (32.0%)	
	Never	59 (44.7%)	514 (36.4%)		36 (45.0%)	537 (36.6%)	
Alcohol (Exam 4)	≥3 a day	21 (15.9%)	241 (17.1%)	0.53	16 (20.0%)	246 (16.8%)	0.41
	1 to 2 a day	50 (37.9%)	457 (32.4%)		30 (37.5%)	477 (32.6%)	
	< 1 a day	9 (6.8%)	133 (9.4%)		4 (5.0%)	138 (9.4%)	
	Non-Drinker	52 (39.4%)	581 (41.2%)		30 (37.5%)	603 (41.2%)	
IR (HOMA)	Yes	71 (53.8%)	879 (62.3%)	0.06	42 (52.5%)	908 (62.0%)	0.09
IR (McAuley)	Yes	33 (25.0%)	545 (38.7%)	0.002	20 (25.0%)	558 (39.1%)	0.02
IR (Combined)	Yes	33 (25.0%)	517 (36.6%)	0.008	20 (25.0%)	530 (36.2%)	0.04

Table 3
Estimated adjusted associations (Odds Ratios (OR) and 95% confidence intervals (CI)) of incident dementia by insulin resistance status using the HOMA/McAuley/Combined indices: results of multivariable logistic regression analysis.

Insulin resistance (IR) index	IR status	No. of subjects	No. of dementia cases	Unadjusted odds ratios (95% CI)	Model 1[a] odds ratio (95% CI)	Model 2[b] odds ratio 95% CI)	Model 3[c] odds ratio (95% CI)
HOMA	Yes	950	71	0.71 (0.49–1.01)	0.86 (0.57–1.29)	0.84 (0.56–1.26)	0.83 (0.55–1.23)
	No	594	61	Referent	Referent	Referent	Referent
McAuley	Yes	578	33	0.53 (0.35–0.80)	0.61 (0.39–0.94)	0.59 (0.38–0.92)	0.58 (0.37–0.91)
	No	966	99	Referent	Referent	Referent	Referent
Combined	Yes	550	33	0.58 (0.38–0.87)	0.66 (0.42–1.03)	0.65 (0.41–1.01)	0.64 (0.41–1.0)
	No	994	99	Referent	Referent	Referent	Referent

[a] Analyses were adjusted for age, BMI, smoking, alcohol, change in total cholesterol.
[b] Analyses were adjusted for age, BMI, smoking, alcohol, change in total cholesterol, prevalent hypertension at Exam 4.
[c] Analyses were adjusted for age, WC, smoking, alcohol, change in total cholesterol, prevalent hypertension at Exam 4.

Table 4
Estimated adjusted associations (Odds Ratios (OR) and 95% confidence intervals (CI)) of incident dementia by insulin resistance status using the Combined index: results of stratified multivariable logistic regression analysis by APOE ε4, hypertension, and coronary heart disease.

Stratified variables		IR status	No of cases	Adjusted odds ratios[a] (95% CI)
APOE ε4	Yes (n = 274)	Yes (n = 109)	8	0.70 (0.27–1.85)
		No (n = 165)	19	Referent
	No (n = 1270)	Yes (n = 421)	25	0.63 (0.38–1.04)
		No (n = 829)	80	Referent
Hypertension	Yes (n = 1106)	Yes (n = 432)	30	0.70 (0.43–1.13)
		No (n = 674)	73	Referent
	No (n = 438)	Yes (n = 118)	3	0.39 (0.11–1.47)
		No (n = 320)	26	Referent
Coronary heart disease	Yes (n = 255)	Yes (n = 106)	6	0.58 (0.20–1.70)
		No (n = 149)	16	Referent
	No (n = 1289)	Yes (n = 444)	27	0.67 (0.41–1.09)
		Yes (n = 845)	83	Referent

[a] Analyses were adjusted for age, BMI, smoking, alcohol, change in total cholesterol.

Table 5
Estimated adjusted associations (Odds Ratios (OR) and 95% confidence intervals (CI)) of Alzheimer's disease by insulin resistance status using the Combined index: results of stratified multivariable logistic regression analysis by APOE ε4, hypertension, and coronary Heart Disease.

Stratified variables		IR status	No of cases	Adjusted odds ratios[a] (95% CI)
APOE ε4	Yes (n = 274)	Yes (n = 109)	5	0.79 (0.23–2.74)
		No (n = 165)	10	Referent
	No (n = 1270)	Yes (n = 441)	15	0.63 (0.33–1.19)
		No (n = 829)	50	Referent
Hypertension	Yes (n = 1106)	Yes (n = 432)	18	0.79 (0.43–1.46)
		No (n = 674)	41	Referent
	No (n = 438)	Yes (n = 118)	2	0.30 (0.06–1.47)
		No (n = 320)	19	Referent
Coronary heart disease	Yes (n = 253)	Yes (n = 106)	4	1.40 (0.32–6.14)
		No (n = 149)	6	Referent
	No (n = 1289)	Yes (n = 444)	16	0.58 (0.32–1.08)
		No (n = 845)	54	Referent

[a] Analyses were adjusted for age, BMI, smoking, alcohol, change in total cholesterol.

Impaired insulin signaling in the brain is most strongly thought to affect the formation of Tau NFTs, aggregation of Aβpp and Aβ, presence of oxidative stress, endoplasmic reticulum (ER) stress, and metabolic dysfunction [12,48–53]. However, these conditions exist after many years of IR conditions. Our restriction of this study cohort by eliminating prevalent type 2 diabetics limits studying the effect of long term insulin resistance. Exams 4 and 5 were separated by 3 years, which may prove to be insufficient time for IR to negatively affect insulin signaling in the brain.

But this short term state of hyperinsulemia can provide a short term positive effect on memory and brain function. Insulin signaling in the brain declines with advanced age [54]. Craft et al. showed increased performance in memory tests in slightly demented AD patients in an induced hyperinsulemic state through intravenous injection of insulin [55]. Intra-nasal administration of insulin has also resulted in significant memory improvement [56]. This suggested the protective effect of hyperinsulimia might explain why our IR subjects who were free of diabetes had an even lower OR of incident dementia and incident AD.

Similar situations with mid and late life cholesterol, blood pressure, and BMI occur where higher later life levels of those three risk factors are actually protective for AD and dementia [57,58]. Therefore, hyperinsulemia and short term IR may actually be an indicator of better health status in the elderly. Fujita et al. showed hyperinsulemia is necessary to stimulate skeletal muscle protein anabolism in the elderly [59]. Similarly, elevated blood pressure in midlife is considered a risk factor for dementia, yet blood pressure was lower in demented patients in older life than non-demented Japanese-American men [32]. Additionally, in a study of the oldest-old, patients who developed hypertension between 80 and 89 years of age had a lower dementia risk (HR 0.58 95% CI 0.34–0.98) compared to subjects without hypertension [60].

Our subjects with the APOE ε4 allele had a 15% increase in odds of dementia and AD, confirming results from previous studies that carriers of the APOE ε4 allele are at greater risk of dementia and AD [61,62]. After stratification by APOE ε4, subjects who did not have the APOE ε4 allele had odds ratios that were higher than those who did have the APOE ε4 allele (Combined Index), however both OR were still < 1. A study conducted by Peila et al. [44] in the Kuakini HHP found that subjects with both type 2 diabetes and the APOE ε4 allele had increased risk for AD (RR 5.5 95% CI 2.2–13.7). The existence of contradictory results show that further research is needed [15,21,63]. Recent studies are showing a lack of interaction between IR and the APOE ε4 allele. Ragogna et al. [64] concluded no relationship between IR, using multiple IR indices, and APOE ε4. Schrijvers et al. [14] did not find a multiplicative nor an additive interaction between HOMA and APOE ε4, and a study by Willette et al. [65] failed to find significant interaction between HOMA and the APOE ε4 allele.

This study has some important strengths. First, the Kuakini HAAS was restricted to men of the same age and ethnicity, which reduced confounding by age, disease, sex-related factors and genetic factors. While recall bias is still possible, the longitudinal nature of this study decreases the chances of recall bias. Unlike previous studies that used HOMA and fasting insulin as indicators of IR, this study utilized the McAuley Index. The McAuley Index is the IR index best suited for epidemiological studies and this was the first use of the McAuley Index to examine IR and incident AD and dementia in a Japanese population [27]. While HOMA and fasting insulin are easily calculated, those indices do not account for triglyceride levels. Elevated triglycerides is one

of the criterion for the Metabolic Syndrome (MetS), and MetS is associated with increased risk of AD [66,67]. The McAuley index is the only IR index that uses triglyceride levels, and allows for the adjustment for the effect of triglycerides on AD.

4.1. Limitations

Some limitations exist in this study. Unfortunately, repeated measurements of IR were not available during subsequent cognitive examinations. It is possible for subjects with IR to revert back to normal levels, which may affect the odds estimates. Of the 1544 patients at exam 4 who were not diabetic, only 39 (2.5%) patients were diagnosed with diabetes three years later during examination 5. Also, we lacked the samples needed to study midlife effects of IR on AD to confirm whether a difference exists between effects of midlife IR and later-life IR on AD. Although recall bias was greatly minimized due to IR classification using results from laboratory testing, recall bias is still possible regarding alcohol and smoking history. The use of midlife smoking status limits the effect of non-differential misclassification of AD and dementiaMisclassification of Alcohol consumption at exam 4 would also be non-differential with respect to AD and dementia status. Future studies would benefit from using cotinine and alcohol specific biomarkers to more accurately determine smoking and alcohol usage. While the restrictions by age, ethnicity and gender reduces confounding, this also limits the generalizability of this study. Additionally, the possibility of survival bias also exists, but because of the closeness in age range within our subjects, stratification by age was not feasible.

The use of systemic IR as a proxy for brain IR must be mentioned as a possible limitation. While a direct causal relationship between systemic and brain IR has not yet been determined, prior studies have shown that systemic IR does affect the flow of insulin into the brain via the blood brain barrier, affecting downstream insulin signaling [68]. Finally, while a previous study confirming clinical AD diagnosis with autopsys analysis found 65% of clinically diagnosed AD cases had sufficient NP to meet neuropathological criteria in the Kuakini HAAS, the possibility of misclassification exists.

Further studies are required to elucidate the relationship between late-life IR and incident AD and dementia and compare them to our understanding of midlife IR and AD. In the future, the use of multiple IR indices, including the McAuley Index, may provide increased accuracy in determining IR status.

Acknowledgments

No potential conflicts of interest relevant to this article were reported.

The authors thank the staff and participants of the Kuakini Honolulu Heart Program for their valuable contributions.

T.L researched data and wrote the manuscript. E.H. contributed to the discussion and reviewed/edited the manuscript. R.C. contributed to the discussion and reviewed/edited the manuscript. Y.Y.W. contributed to the discussion and reviewed/edited the manuscript. C.W. reviewed and edited the manuscript. K.M. collected data and reviewed/edited the manuscript. A.G. contributed to the discussion and reviewed/edited the manuscript.

References

[1] United Nations DoEaSA, Population Division World Population Aging 2013, (2013).
[2] Association As, 2014 Alzheimer's disease facts and figures, Alzheimers Dement. 10 (2) (2014).
[3] C.P. Ferri, M. Prince, C. Brayne, H. Brodaty, L. Fratiglioni, M. Ganguli, et al., Global prevalence of dementia: a Delphi consensus study, Lancet (London, England) 366 (9503) (2005) 2112–2117.
[4] R. Brookmeyer, E. Johnson, K. Ziegler-Graham, H.M. Arrighi, Forecasting the global burden of Alzheimer's disease, Alzheimers Dement. 3 (3) (2007) 186–191.
[5] C.L. Leibson, W.A. Rocca, V.A. Hanson, R. Cha, E. Kokmen, P.C. O'Brien, et al., Risk of dementia among persons with diabetes mellitus: a population-based cohort study, Am. J. Epidemiol. 145 (4) (1997) 301–308.
[6] A. Ott, R.P. Stolk, F. van Harskamp, H.A. Pols, A. Hofman, M.M. Breteler, Diabetes mellitus and the risk of dementia: the Rotterdam study, Neurology 53 (9) (1999) 1937–1942.
[7] W. Xu, C. Qiu, M. Gatz, N.L. Pedersen, B. Johansson, L. Fratiglioni, Mid- and late-life diabetes in relation to the risk of dementia: a population-based twin study, Diabetes 58 (1) (2009) 71–77.
[8] F. Irie, A.L. Fitzpatrick, O.L. Lopez, L.H. Kuller, R. Peila, A.B. Newman, et al., Enhanced risk for Alzheimer disease in persons with type 2 diabetes and APOE epsilon4: the cardiovascular health study cognition study, Arch. Neurol. 65 (1) (2008) 89–93.
[9] S.M. de la Monte, J.R. Wands, Alzheimer's disease is type 3 diabetes-evidence reviewed, J. Diabetes Sci. Technol. 2 (6) (2008) 1101–1113.
[10] B. Cholerton, L.D. Baker, S. Craft, Insulin, cognition, and dementia, Eur. J. Pharmacol. 719 (1–3) (2013) 170–179.
[11] A. Kleinridders, H.A. Ferris, W. Cai, C.R. Kahn, Insulin action in brain regulates systemic metabolism and brain function, Diabetes 63 (7) (2014) 2232–2243.
[12] F.G. De Felice, M.V. Lourenco, S.T. Ferreira, How does brain insulin resistance develop in Alzheimer's disease? Alzheimer's Dement. J. Alzheimer's Assoc.. 10 (1 Suppl) (2014) S26–S32.
[13] G. Wilcox, Insulin and insulin resistance, Clin. Biochem. Rev. 26 (2) (2005) 19–39.
[14] E.M. Schrijvers, J.C. Witteman, E.J. Sijbrands, A. Hofman, P.J. Koudstaal, M.M. Breteler, Insulin metabolism and the risk of Alzheimer disease: the Rotterdam study, Neurology 75 (22) (2010) 1982–1987.
[15] E. Ronnemaa, B. Zethelius, J. Sundelof, J. Sundstrom, M. Degerman-Gunnarsson, C. Berne, et al., Impaired insulin secretion increases the risk of Alzheimer disease, Neurology 71 (14) (2008) 1065–1071.
[16] S.L. Syme, M.G. Marmot, A. Kagan, H. Kato, G. Rhoads, Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: introduction, Am. J. Epidemiol. 102 (6) (1975) 477–480.
[17] L.A. Pedrini, De Cristofaro, V, Comelli M, casino FG, Prencipe M, Baroni a, et al. long-term effects of high-efficiency on-line haemodiafiltration on uraemic toxicity. A multicentre prospective randomized study, Nephrol. Dial. Transplant. Off. Publ. Eur. Dial. Transplant. Assoc. Eur. Ren. Assoc.. 26 (8) (2011) 2617–2624.
[18] L. White, H. Petrovitch, G.W. Ross, K.H. Masaki, R.D. Abbott, E.L. Teng, et al., Prevalence of dementia in older Japanese-American men in Hawaii: the Honolulu-Asia aging study, Jama 276 (12) (1996) 955–960.
[19] E.L. Teng, K. Hasegawa, A. Homma, Y. Imai, E. Larson, A. Graves, et al., The cognitive abilities screening instrument (CASI): a practical test for cross-cultural epidemiological studies of dementia, Int. Psychogeriatr./IPA 6 (1) (1994) 45–58 (discussion 62).
[20] R.J. Havlik, G. Izmirlian, H. Petrovitch, G.W. Ross, K. Masaki, J.D. Curb, et al., APOE-epsilon4 predicts incident AD in Japanese-American men: the Honolulu-asia aging study, Neurology 54 (7) (2000) 1526–1529.
[21] R. Peila, B.L. Rodriguez, L.J. Launer, Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: the Honolulu-Asia aging study, Diabetes 51 (4) (2002) 1256–1262.
[22] G. McKhann, D. Drachman, M. Folstein, R. Katzman, D. Price, E.M. Stadlan, Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease, Neurology 34 (7) (1984) 939–944.
[23] M. Gearing, S.S. Mirra, J.C. Hedreen, S.M. Sumi, L.A. Hansen, A. Heyman, The consortium to establish a registry for Alzheimer's disease (CERAD). Part X. neuropathology confirmation of the clinical diagnosis of Alzheimer's disease, Neurology 45 (3 Pt 1) (1995) 461–466.
[24] H. Petrovitch, L.R. White, G.W. Ross, S.C. Steinhorn, C.Y. Li, K.H. Masaki, et al., Accuracy of clinical criteria for AD in the Honolulu-Asia aging study, a population-based study, Neurology 57 (2) (2001) 226–234.
[25] H. Yokoyama, M. Emoto, S. Fujiwara, K. Motoyama, T. Morioka, M. Komatsu, et al., Quantitative insulin sensitivity check index and the reciprocal index of homeostasis model assessment in normal range weight and moderately obese type 2 diabetic patients, Diabetes Care 26 (8) (2003) 2426–2432.
[26] P.A. Sarafidis, A.N. Lasaridis, P.M. Nilsson, M.I. Pikilidou, P.C. Stafilas, A. Kanaki, et al., Validity and reproducibility of HOMA-IR, 1/HOMA-IR, QUICKI and McAuley's indices in patients with hypertension and type II diabetes, J. Hum. Hypertens. 21 (9) (2007) 709–716.
[27] M. Gutch, S. Kumar, S.M. Razi, K.K. Gupta, A. Gupta, Assessment of insulin sensitivity/resistance, Indian J. Endocrinol. Metab.. 19 (1) (2015) 160–164.
[28] L.A. Farrer, L.A. Cupples, J.L. Haines, B. Hyman, W.A. Kukull, R. Mayeux, et al., Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer disease Meta analysis consortium, Jama 278 (16) (1997) 1349–1356.
[29] J.E. Hixson, D.T. Vernier, Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI, J. Lipid Res. 31 (3) (1990) 545–548.
[30] C.A. Hostage, K. Roy Choudhury, P.M. Doraiswamy, J.R. Petrella, Dissecting the gene dose-effects of the APOE epsilon4 and epsilon2 alleles on hippocampal volumes in aging and Alzheimer's disease, PLoS ONE 8 (2) (2013) e54483.
[31] L.J. Launer, G.W. Ross, H. Petrovitch, K. Masaki, D. Foley, L.R. White, et al., Midlife blood pressure and dementia: the Honolulu-Asia aging study, Neurobiol. Aging 21 (1) (2000) 49–55.
[32] K.L. Edwards, C.M. Burchfiel, D.S. Sharp, J.D. Curb, B.L. Rodriguez, W.Y. Fujimoto, et al., Factors of the insulin resistance syndrome in nondiabetic and diabetic elderly Japanese-American men, Am. J. Epidemiol. 147 (5) (1998) 441–447.
[33] S.P. Kennelly, B.A. Lawlor, R.A. Kenny, Blood pressure and dementia - a comprehensive review, Ther. Adv. Neurol. Disord. 2 (4) (2009) 241–260.
[34] S. Kalmijn, D. Foley, L. White, C.M. Burchfiel, J.D. Curb, H. Petrovitch, et al.,

Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men. The Honolulu-Asia aging study, Arterioscler. Thromb. Vasc. Biol. 20 (10) (2000) 2255–2260.
[35] H. Ohnishi, S. Saitoh, S. Takagi, N. Katoh, Y. Chiba, H. Akasaka, et al., Incidence of type 2 diabetes in individuals with central obesity in a rural Japanese population: the Tanno and Sobetsu study, Diabetes Care 29 (5) (2006) 1128–1129.
[36] H. Ohnishi, S. Saitoh, S. Takagi, J. Ohata, H. Takeuchi, T. Isobe, et al., Incidence of insulin resistance in obese subjects in a rural Japanese population: the Tanno and Sobetsu study, Diabetes Obes. Metab. 7 (1) (2005) 83–87.
[37] M. Bajaj, Nicotine and insulin resistance: when the smoke clears, Diabetes 61 (12) (2012) 3078–3080.
[38] T. Ohara, T. Ninomiya, J. Hata, M. Ozawa, D. Yoshida, N. Mukai, et al., Midlife and late-life smoking and risk of dementia in the community: the Hisayama study, J. Am. Geriatr. Soc. 63 (11) (2015) 2332–2339.
[39] D.J. Galanis, C. Joseph, K.H. Masaki, H. Petrovitch, G.W. Ross, L. White, A longitudinal study of drinking and cognitive performance in elderly Japanese American men: the Honolulu-Asia aging study, Am. J. Public Health 90 (8) (2000) 1254–1259.
[40] R. Stewart, L.R. White, Q.L. Xue, L.J. Launer, Twenty-six-year change in total cholesterol levels and incident dementia: the Honolulu-Asia aging study, Arch. Neurol. 64 (1) (2007) 103–107.
[41] T. Hayashi, E.J. Boyko, M.J. McNeely, D.L. Leonetti, S.E. Kahn, W.Y. Fujimoto, Minimum waist and visceral fat values for identifying Japanese Americans at risk for the metabolic syndrome, Diabetes Care 30 (1) (2007) 120–127.
[42] D.R. Taaffe, F. Irie, K.H. Masaki, R.D. Abbott, H. Petrovitch, G.W. Ross, et al., Physical activity, physical function, and incident dementia in elderly men: the Honolulu-Asia aging study, J. Gerontol. A Biol. Sci. Med. Sci. 63 (5) (2008) 529–535.
[43] R.V. Acuff, D.J. Cai, Z.P. Dong, D. Bell, The lipid lowering effect of plant sterol ester capsules in hypercholesterolemic subjects, Lipids Health Dis. 6 (2007) 11.
[44] R. Peila, B.L. Rodriguez, L.R. White, L.J. Launer, Fasting insulin and incident dementia in an elderly population of Japanese-American men, Neurology 63 (2) (2004) 228–233.
[45] T. Matsuzaki, K. Sasaki, Y. Tanizaki, J. Hata, K. Fujimi, Y. Matsui, et al., Insulin resistance is associated with the pathology of Alzheimer disease: the Hisayama study, Neurology 75 (9) (2010) 764–770.
[46] J. Kuusisto, K. Koivisto, L. Mykkanen, E.L. Helkala, M. Vanhanen, T. Hanninen, et al., Association between features of the insulin resistance syndrome and Alzheimer's disease independently of apolipoprotein E4 phenotype: cross sectional population based study, BMJ (Clin. Res. Ed.) 315 (7115) (1997) 1045–1049.
[47] M. Thambisetty, E. Jeffrey Metter, A. Yang, H. Dolan, C. Marano, A.B. Zonderman, et al., Glucose intolerance, insulin resistance, and pathological features of Alzheimer disease in the Baltimore longitudinal study of aging, JAMA Neurol. 70 (9) (2013) 1167–1172.
[48] S.M. de la Monte, M. Tong, Brain metabolic dysfunction at the core of Alzheimer's disease, Biochem. Pharmacol. 88 (4) (2014) 548–559.
[49] S.M. de la Monte, Insulin resistance and Alzheimer's disease, BMB Rep. 42 (8) (2009) 475–481.
[50] A. Jones, P. Kulozik, A. Ostertag, S. Herzig, Common pathological processes and transcriptional pathways in Alzheimer's disease and type 2 diabetes, J. Alzheimer's Dis. JAD 16 (4) (2009) 787–808.
[51] B. Medhi, M. Chakrabarty, Insulin resistance: an emerging link in Alzheimer's disease, Neurol. Sci. Off. J. Ital. Neurol. Soc. Ital. Soc. Clin. Neurophysiol.. 34 (10) (2013) 1719–1725.
[52] D.A. Butterfield, F. Di Domenico, E. Barone, Elevated risk of type 2 diabetes for development of Alzheimer disease: a key role for oxidative stress in brain, Biochim. Biophys. Acta 1842 (9) (2014) 1693–1706.
[53] C. Benedict, S.J. Brooks, J. Kullberg, J. Burgos, M.J. Kempton, R. Nordenskjold, et al., Impaired insulin sensitivity as indexed by the HOMA score is associated with deficits in verbal fluency and temporal lobe gray matter volume in the elderly, Diabetes Care 35 (3) (2012) 488–494.
[54] G.M. Cole, S.A. Frautschy, The role of insulin and neurotrophic factor signaling in brain aging and Alzheimer's disease, Exp. Gerontol. 42 (1–2) (2007) 10–21.
[55] S. Craft, J. Newcomer, S. Kanne, S. Dagogo-Jack, P. Cryer, Y. Sheline, et al., Memory improvement following induced hyperinsulinemia in Alzheimer's disease, Neurobiol. Aging 17 (1) (1996) 123–130.
[56] C. Benedict, M. Hallschmid, K. Schmitz, B. Schultes, F. Ratter, H.L. Fehm, et al., Intranasal insulin improves memory in humans: superiority of insulin aspart, Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol.. 32 (1) (2007) 239–243.
[57] M.C. Morris, P.A. Scherr, L.E. Hebert, R.J. Glynn, D.A. Bennett, D.A. Evans, Association of incident Alzheimer disease and blood pressure measured from 13 years before to 2 years after diagnosis in a large community study, Arch. Neurol. 58 (10) (2001) 1640–1646.
[58] E. Barrett-Connor, S.L. Edelstein, J. Corey-Bloom, W.C. Wiederholt, Weight loss precedes dementia in community-dwelling older adults, J. Am. Geriatr. Soc. 44 (10) (1996) 1147–1152.
[59] S. Fujita, E.L. Glynn, K.L. Timmerman, B.B. Rasmussen, E. Volpi, Supraphysiological hyperinsulinaemia is necessary to stimulate skeletal muscle protein anabolism in older adults: evidence of a true age-related insulin resistance of muscle protein metabolism, Diabetologia 52 (9) (2009) 1889–1898.
[60] M.M. Corrada, K.M. Hayden, A. Paganini-Hill, S.S. Bullain, J. DeMoss, C. Aguirre, et al., Age of onset of hypertension and risk of dementia in the oldest-old: the 90+ study, Alzheimer's Dement. J. Alzheimer's Assoc. 13 (2) (2017) 103–110.
[61] J.H. Chen, K.P. Lin, Y.C. Chen, Risk factors for dementia, J. Formos. Med. Assoc. = Taiwan yi zhi 108 (10) (2009) 754–764.
[62] M. Kivipelto, S. Rovio, T. Ngandu, I. Kareholt, M. Eskelinen, B. Winblad, et al., Apolipoprotein E epsilon4 magnifies lifestyle risks for dementia: a population-based study, J. Cell. Mol. Med. 12 (6b) (2008) 2762–2771.
[63] C.C. Liu, T. Kanekiyo, H. Xu, G. Bu, Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy, Nat. Rev. Neurol. 9 (2) (2013) 106–118.
[64] F. Ragogna, G. Lattuada, G. Ruotolo, L. Luzi, G. Perseghin, Lack of association of apoE epsilon4 allele with insulin resistance, Acta Diabetol. 49 (1) (2012) 25–32.
[65] A.A. Willette, B.B. Bendlin, E.J. Starks, A.C. Birdsill, S.C. Johnson, B.T. Christian, et al., Association of Insulin Resistance with Cerebral Glucose Uptake in late middle-aged adults at risk for Alzheimer disease, JAMA Neurol. 72 (9) (2015) 1013–1020.
[66] M. Vanhanen, K. Koivisto, L. Moilanen, E.L. Helkala, T. Hanninen, H. Soininen, et al., Association of metabolic syndrome with Alzheimer disease: a population-based study, Neurology 67 (5) (2006) 843–847.
[67] G. Razay, A. Vreugdenhil, G. Wilcock, The metabolic syndrome and Alzheimer disease, Arch. Neurol. 64 (1) (2007) 93–96.
[68] S.E. Arnold, Z. Arvanitakis, S.L. Macauley-Rambach, A.M. Koenig, H.Y. Wang, R.S. Ahima, et al., Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums, Nat. Rev. Neurol. 14 (3) (2018) 168–181.