

Original Article

Cognitive impairment and limited dietary diversity or physical inactivity are conjoint precursors of incident diabetes more so in elderly women than men

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OBJECTIVES: To establish whether elderly people with impaired cognition are at greater risk for the development of type 2 diabetes. **DESIGN:** Prospective population-based cohort study. **SETTING:** The Elderly Nutrition and Health Survey in Taiwan (NAHSIT Elderly). **PARTICIPANTS:** One thousand and four hundred ninety-three diabetes-free people ≥ 65 years were followed for incident diabetes in relation to cognitive status for up to 8 years. **MEASUREMENTS:** The association between cognitive impairment and diabetes incidence was analyzed with Cox proportional hazards models with exclusion of people who had diabetes within one year of cognitive function assessments. **RESULTS:** Cognitively-impaired women, but not men, had increased diabetes incidence density (DID). Age, gender, ethnicity and personal behavior adjusted hazard ratios (HR) and 95% confidence intervals (CI) for type 2 diabetes with normal cognition as referent were 2.43 (95% CI: 1.27-4.63) for women and 1.55 (95% CI: 0.48-5.07) for men. These gender differences and the HR significances remained with adjustments for age, ethnicity, financial status, dietary quality as a dietary diversity score, physical functioning, physical activity, fasting glucose, indices of body composition, body mass index, waist circumference, mid-arm muscle circumference, perceived and mental health status. There were extensive significant interactions with the covariates in women. **CONCLUSION:** Cognitive impairment in later life is associated with greater risk of type 2 diabetes in women and considerable potential risk enhancement.

Key Words: cognitive impairment, type 2 diabetes, dietary, physical activity, body composition

INTRODUCTION

The prevalences of both cognitive impairment and diabetes increase with age.^{1,2} It is clear that diabetes can be an antecedent and risk factor for cognitive impairment,^{3,4} dementia⁵ and affective disorders⁶ associated with neurodegeneration. However, the extent to which impaired cognition might be a risk factor for diabetes is unclear or not canvassed in the observed associations between the two.^{7,8} For the neurodegenerative Parkinson's disease⁹ and for affective disorders like depression,⁶ there would appear to be a bidirectional pathogenesis with diabetes.¹⁰ It is plausible that cognitive impairment might increase the risk of diabetes by way of poor food and activity choices,¹¹ through neuro-endocrine pathways activated in stress and adversely affecting visceral fat¹² or via a shared underlying pathology which might include stress hormones known both to compromise cognition and increase insulin resistance.¹³ At the least, the presence of cognitive impairment might modulate recognized risk factors for diabetes such as pre-diabetes, diet, physical activity, body

composition or mental health (Figure 1).

Our general hypothesis is that elderly people with impaired cognition are at greater risk for the development of type 2 diabetes (T2DM). Therefore, we have assessed in a Taiwanese cohort whether elderly people who have impaired cognition have a higher incidence of diabetes.

RESEARCH DESIGN AND METHODS

Data used in this study were from the Elderly Nutrition

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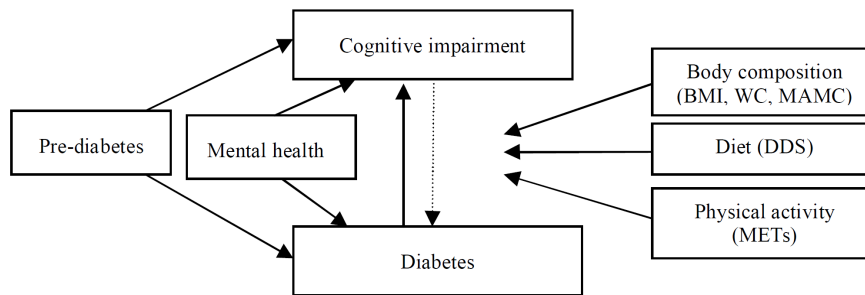


Figure 1. An hypothesis that not only does diabetes increase the risk of cognitive impairment, but that the reverse may also apply or that both may have an underlying pathogenesis, in any case modulated by contributors to energy nutrition (diet and physical activity).

and Health Survey (NAHSIT Elderly) which is a nationally representative sample of the free-living elderly, aged 65 and over, conducted during 1999 and 2000 in Taiwan. A multi-staged, stratified, systematic sampling scheme was used in the survey. The interview information (which included self-reports) was collected in households, face to face.¹⁴ The dataset was linked to the 1999-2006 National Health Insurance to assess T2DM incidence.

Participants

There were 1,937 participants who completed the household interview; 49 had no cognition or dietary data and were excluded. An additional 395 participants were excluded on account of diabetes diagnosis before or within the first year of interview. Finally, a total of 1,493 elders were studied. All participants signed informed consent. To ensure anonymity, coding was subject to a double-scrambling procedure. The ethics committees of the National Health Research Institutes and of Academia Sinica approved the study protocol.

Cognitive function

Cognitive function was assessed by the Short Portable Mental Status Questionnaire (SPMSQ) which has been validated in Chinese, in a Taiwanese population.¹⁵ This test has 10 questions dealing with orientation in time and place, personal history, long term and short-term memory and calculation. In this test, total score ranges from zero to ten. Correct answers were coded 1, whereas errors were coded 0. Participants were grouped into normal, those who did not incur errors (SPMSQ score is 10 for intact cognition), and impaired cognition where one or more errors was incurred.

Type 2 diabetes (T2DM)

The presence of T2DM was recognized by the diagnostic codes A181 (Taiwan), pre-ICD9 use before 2000, or by ICD-9 Code 250, without evidence of insulin dependency (eg, ketoacidosis). At least two diabetes mellitus records within one year were required. Unless otherwise indicated, in this report we mean T2DM when we refer to diabetes.

Dietary Diversity Score, DDS

Dietary quality was measured by DDS. From a 24-hour recall, a DDS (range 1-6) was derived, a modification of the NHANES method.¹⁶ In accordance with the Taiwanese Food Guides, half a serving per day for one of the six food groups including 'dairy', 'meat', 'staple', 'fruit', 'vegetable' and 'fat and oil' was the minimal intake required for a DDS score of 1. The 'meat' group comprised

protein rich foods, ie eggs, fish and shellfish, soybean products and meats. Higher scores indicate better quality.

Physical function and mental health

A validated traditional Chinese version (a Short Form, SF-36[®]) was used to assess physical function and mental health. SF-36 contains a total of 36 items with self-assessment questions to measure eight dimensions of health, which included physical functioning (PF) and mental health.^{17,18,24} We grouped subjects' responses into eight subscales following the norm-based scoring system ($\mu=50$, $\sigma=10$) and calculated the standardized score for each subscale on the basis of the NAHSIT population.^{17,25} We used the physical functioning and mental health scores as our measure of physical function and mental health, respectively. We further classified mental health by tertile, approximations in this population as <48, 48-55, >55.¹⁵

Physical activity

Daily physical activity was measured by the number of metabolic equivalents (METs) calculated from sport and leisure time activities, based on activity duration, frequency and intensity, as well as the number of stairs climbed.¹⁹

Fasting glucose, FG

Impaired fasting glucose (IFG) was defined by an elevated fasting plasma glucose (FPG) concentration (100-125 mg/dL) in accordance with American Diabetes Association criteria.²⁰

Body composition

After an overnight fast, height and weight were measured without shoes and with a deduction for estimated clothes' weight. Waist circumference (WC in cm) was measured at the level of the natural waist. Mid-arm circumference (MAC in cm) was measured midway between the acromion and the olecranon with the arm parallel to the trunk. With Lange skinfold calipers, triceps skinfold (TSF in mm) thickness was measured midway between the acromion and the olecranon on the mid-line of the posterior of the right upper arm.^{14,17} Mid-arm muscle circumference (MAMC in cm) = $MAC - (\pi \times TSF)$ ²¹ was used as an index of relative sarcopenia. Central obesity was defined for men as a $WC \geq 90$ and, for women, a $WC \geq 80$, according to Taiwanese criteria based on Asian recommendations by the WHO,^{22,23} MAMC was considered as gender-specific distribution tertiles.¹⁷

Table 1. Demographic and personal behavioral variables by cognitive status in NAHSIT Elderly.^{†‡} (n=1,493)

Variables	Men (n=767) (%)				Women (n=726) (%)			
	Total	Normal	Cognitive impairment	<i>p</i> value	Total	Normal	Cognitive impairment	<i>p</i> value
Baseline intragender prevalence (%)		90.2	9.84		72.5		27.5	
Baseline whole population prevalence (%)		46.5	4.89		34.4		14.3	
Age, yrs (%)				0.003				<0.001
65-69	28.5	30.6	10.1		30.4	34.9	18.7	
70-74	32.1	33.7	17.5		29.3	31.2	24.0	
75-97	39.4	35.8	72.4		40.3	33.9	57.3	
Education (%)				<0.001				<0.001
Illiterate	21.7	18.8	48.4		59.0	49.8	83.3	
Elementary school and below	47.3	48.0	40.8		29.7	35.1	15.4	
High school and college	30.7	33.2	7.6		10.5	14.0	1.38	
Ethnicity (%)				0.01				0.09
Non indigenous	98.0	98.2	95.6		97.6	98.0	96.7	
Indigenous	2.0	1.76	4.39		2.24	1.86	3.27	
Perceived financial status (%)				0.04				0.002
Enough	75.4	77.6	54.8		70.6	75.4	57.7	
Some difficulty	18.4	17.0	31.1		19.9	17.4	26.3	
Very difficult	3.1	2.86	4.98		6.14	4.18	11.3	
Alcohol drinker (%)				0.126				0.158
No	56.6	56.0	62.3		94.6	93.6	97.4	
Former	12.6	12.3	14.6		0.95	1.10	0.58	
Current	30.3	31.5	19.9		4.16	4.97	2.05	
Smoker (%)				0.714				0.449
Never	33.0	32.7	35.5		95.1	94.5	96.4	
Former	26.6	26.4	27.9		1.49	1.82	0.62	
Current	40.1	40.5	36.4		3.19	3.28	2.96	
DDS (%)				0.003				0.003
≤3	14.9	13.4	28.2		18.5	16.0	25.2	
4	31.8	30.2	46.2		31.3	28.2	39.6	
5-6	53.4	56.4	25.6		50.1	55.8	35.3	
Physical functioning (%)				<0.001				<0.001
<45	16.9	11.8	67.0		32.2	24.5	53.1	
45-53.9	28.7	29.7	18.7		35.6	39.2	25.9	
54-57.9	32.2	34.5	9.38		21.9	23.9	16.6	
≥58	22.2	24.0	4.92		10.2	12.4	4.40	
Leisure time physical activity (METs) (%)				0.004				<0.001
<1.5	52.7	50.2	75.3		61.2	55.3	76.7	
1.5-3	11.3	12.0	4.41		12.1	13.3	9.04	
>3	36.1	37.8	20.3		26.7	31.4	14.3	
Perceived health status (%)				0.008				0.007
Good	58.9	61.1	38.8		58.8	63.5	46.6	
Fair	31.5	31.7	29.0		28.1	27.9	28.5	
Poor	9.04	7.09	26.9		12.0	8.03	22.3	
Fasting glucose, mg/dL, mean		104	102	0.7		104	110	0.3
BMI, kg/m ² , mean,		23.3	21.9	0.04		24.0	22.9	0.01
WC, cm, mean		85.2	83.3	0.3		81.1	80.2	0.4
MAMC, cm, mean		23.2	22.2	0.05		21.3	20.8	0.1
Mental health norm based score, mean		52.1	48.7	<0.01		49.8	45.5	<0.001
Duration of diabetes observation, years		7.1	7.4	<0.001		7.0	6.2	0.2
Diabetes incidence density/1000 person-years		257	224	0.09		261	307	<0.001

DM=diabetes.

† % are weighted to reflect their representation in the population.

‡ Chi-square test by SUDAAN program

Statistical analysis

All data were weighted for adequate representation of the elderly population in Taiwan during 1999-2000. Chi-square tests were used for categorical variables across cognitive status groups. Cox proportional-hazards models were used to evaluate the effect of cognitive status on risk

of developing diabetes from 1999 to 2006 with relevant covariate adjustments, including gender, age, education, ethnicity, alcohol drinking and smoking status. Relevance was determined with regard to the current literature on risk for cognitive impairment and on the basis of factors significantly related to cognitive impairment in this popu-

Table 2. Hazards ratio of cognitive impairment on risk of developing diabetes in NAHSIT elderly (n=1,493)

	HR ratio (95% confidence intervals)		
	Normal [†]	Cognitive impaired	<i>p</i> for trend
Crude	1.00	1.78 (1.05-3.02)*	0.03
Model 1	1.00	2.17 (1.23-3.82)**	0.009
Women	1.00	2.43 (1.27-4.63)**	0.009
Men	1.00	1.55 (0.48-5.07)	0.4
Model 2 (Financial)			
Women	1.00	2.05 (1.08-3.87)*	0.03
Men	1.00	1.67 (0.60-4.64)	0.3
Model 3 (DDS)			
Women	1.00	2.44 (1.28-4.62)**	0.008
Men	1.00	1.38 (0.42-4.53)	0.6
Model 4 (PF)			
Women	1.00	2.52 (1.25-5.11)*	0.01
Men	1.00	1.05 (0.23-4.72)	0.9
Model 5 (METs)			
Women	1.00	2.44 (1.36-4.36)**	0.004
Men	1.00	1.55 (0.46-5.22)	0.5
Model 6 (FG)			
Women	1.00	3.87 (1.47-10.21)**	0.008
Men	1.00	0.94 (0.16-5.56)	0.9
Model 7 (BMI)			
Women	1.00	3.50 (1.21-10.18)*	0.02
Men	1.00	2.17 (0.71-6.67)	0.2
Model 8 (WC)			
Women	1.00	4.26 (1.65-11.04)**	0.004
Men	1.00	2.33 (0.63-8.57)	0.2
Model 9 (MAMC)			
Women	1.00	2.65 (1.28-5.49)*	0.01
Men	1.00	1.69(0.52-5.53)	0.4
Model 10 (Mental health)			
Women	1.00	2.23 (1.22-4.08)*	0.01
Men	1.00	1.69 (0.55-5.20)	0.3
Model 11 (Perceived health status)			
Women	1.00	2.45 (1.28-4.68)**	0.009
Men	1.00	1.61 (0.43-6.06)	0.5

[†] Hazards ratios of developing diabetes were estimated by the Cox proportional-hazards model, "Normal" as reference group.

Model 1 adjusted for age (yr), gender, ethnicity, smoking status and drinking; Model 2 adjusted for Model 1 covariates and financial status; Model 3 adjusted for Model 1 covariates and DDS; Model 4 adjusted for Model 1 covariates and physical function; Model 5 adjusted for Model 1 covariates and METs; Model 6 adjusted for Model 1 covariates and FG; Model 7 adjusted for Model 1 covariates and BMI; Model 8 adjusted for Model 1 covariates and WC; Model 9 adjusted for Model 1 covariates and MAMC; Model 10 adjusted for Model 1 covariates and mental health; Model 11 adjusted for Model 1 covariates and Perceived health status.

**p*<0.05, ** *p*<0.01

lation (Table 1). The models were further adjusted on this background for financial status, DDS, physical functioning, METs, FG, body composition, mental health and perceived health status. All analyses were performed using SAS statistical software (version 9.1.3) and SUDAAN (version 10.0).

RESULTS

Socio-demography and personal behaviors

A total of 1,493 participants including 767 men and 726 women were involved in this study. Men and women have different cognition status and diabetes incidence even for the same risk factors, so their characteristics are presented separately. Cognitive impairment prevalence for men and women are 9.8% and 27.5% respectively. Cognitive impairment is significantly associated with age, ethnicity (men only), education, perceived financial status, DDS, physical function, leisure time physical activity, mental health, perceived health and BMI. Older people had a higher risk of cognitive impairment, especially those aged over 75 years. People who had a high school

and college education had a lower risk of cognitive impairment. Other characteristics which are risk factors for diabetes, such as DDS,²⁶ physical function,²⁷ physical activity,²⁸ BMI,²⁹ but not WC,^{30,31} were also significantly associated in the present study with cognitive status. For women, cognitive impairment was associated with a higher risk of T2DM than men. (Table 1)

Cognitive status, gender and risk of diabetes

In Table 2 the hazards ratios (HR) and 95% confidence intervals (CI) for the risk with cognitive impairment of diabetes are shown by gender in a crude model and Models 1 to 11 with various adjustments. Model 1 is the basic model with adjustments for age, gender (where all subjects are considered), ethnicity, smoking status and drinking alcohol. Models 2 to 11 represent adjustments to Model 1. Only in women are the HRs significant and this significance persists with adjustments for financial status, DDS, physical functioning, physical activity, fasting glucose, BMI, WC, MAMC, mental health and perceived health status.

Joint effects on diabetes incidence of ethnicity with cognition

Because of the difference in prevalence of diabetes between indigenous and non-indigenous Taiwanese,³²⁻³⁴ we considered the joint effect of indigenous status and cognition on risk for diabetes. Compared to non-indigenous without cognitive impairment, non-indigenous women with cognitive impairment had an HR of 2.44 with 95% CI of 1.27-4.68; in indigenous men who were not cognitively impaired the HR was 0.64 with 95% CI 0.42-1.00. (Figure 2)

Joint effects of diabetes incidence of perceived health status with cognition

Given the functional and integrative health significance of 'perceived health status', we considered whether it might act conjointly with cognition to alter the risk for diabetes (Figure 2). In cognitively impaired women with poor perceived health status, the HR (95% CI) was 5.55 (2.70-11.41) using women with normal cognition and good perceived health status as referent; the interaction was of borderline significance with $p=0.07$. In men the interaction was non-significant with $p=0.13$.

Joint effects on diabetes incidence by DDS, physical function and physical activity with cognition

Using non-cognitively impaired individuals with, respectively, the highest DDS, physical functioning and physical activity as referent, their joint effects on the risk of diabe-

tes over 8 years are shown in Figure 3. In each case, women who were cognitively impaired exhibited a significant or near-significant interaction (p for DDS is 0.004, for physical functioning is 0.07, and for physical activity is 0.03 with that risk factor such that when it was lowest the risk of diabetes was significantly greatest [HR and 95% CI respectively 13.9 (4.55-42.4), 5.13 (2.06-12.8) and 2.88 (1.12-7.43)]. For men, there were no significant interactions, although, for DDS, intermediate values had the worst risk (HR 3.45, 95% CI: 1.27-9.38), while, for physical functioning, when least the HR was 7.49, 95% CI: 2.22-25.3, in those cognitively impaired.

Joint effects on diabetes incidence of mental health with cognition

Where mental health is least good it is interactive with cognitive impairment for the risk of diabetes in women ($p=0.04$), but not in men. At the same time the HR (95% CI) when there is cognitive impairment and the least good mental health is 2.51 (1.10-5.70) using best case as referent. (Figure 3)

Joint effects on diabetes incidence of body composition with cognition

In Figure 4, fat distribution by WC and muscle mass by MAMC as possible joint risk factors with cognitive impairment for diabetes are shown. In women only are the interactions significant, WC $p=0.02$ and MAMC $p=0.002$. In addition, when there is cognitive impairment, the joint

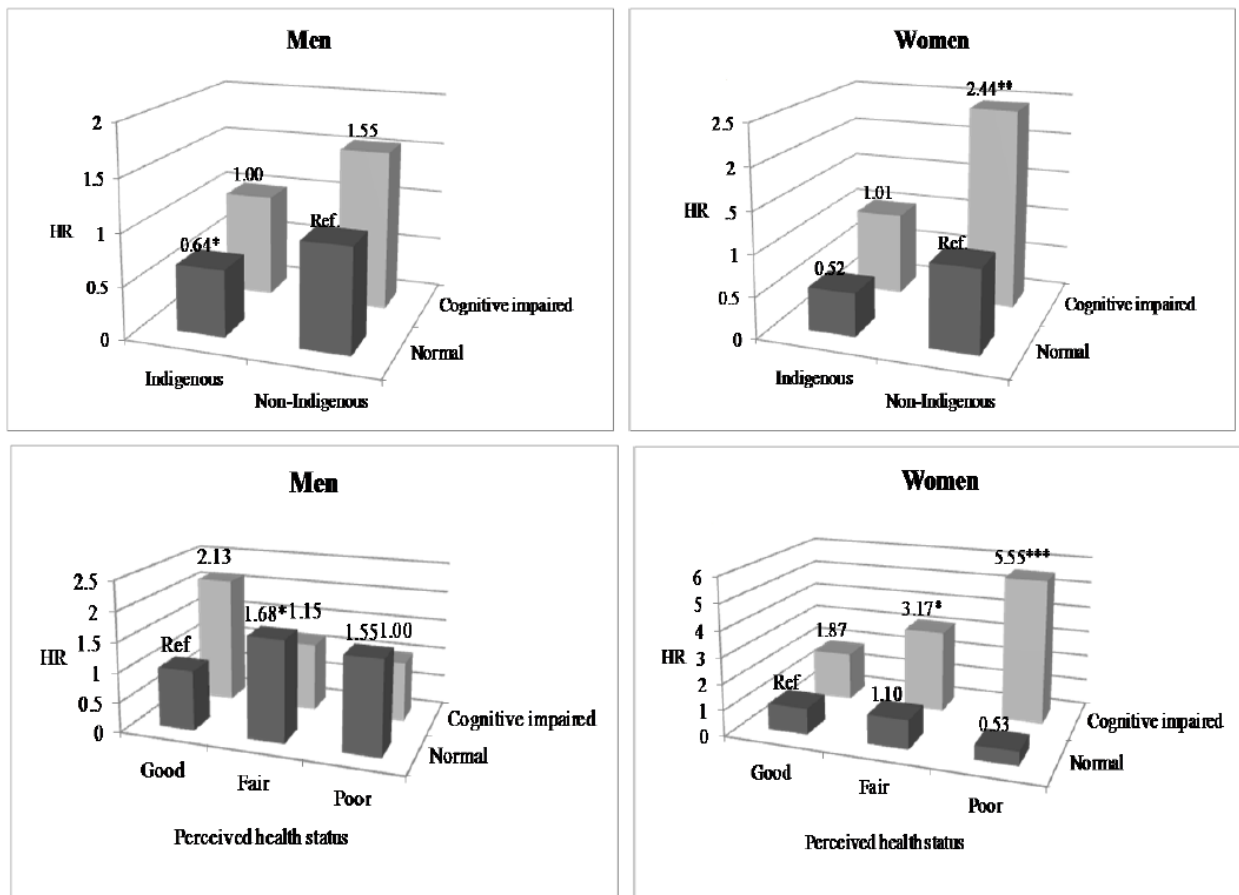


Figure 2. Joint hazard ratios (HRs) for developing diabetes in elder Taiwanese after an 8-year follow-up in accordance with cognitive function and in relation to ethnicity. The model has been adjusted for gender, age, education, alcohol drinking, and smoking. Significance is shown by * $p<0.05$, ** $p<0.01$, *** $p<0.001$. The p value for interaction for cognitive status and ethnicity in men and women are 0.07 and 0.04; for cognitive status and perceived health status in men and women are 0.13 and 0.07 respectively.

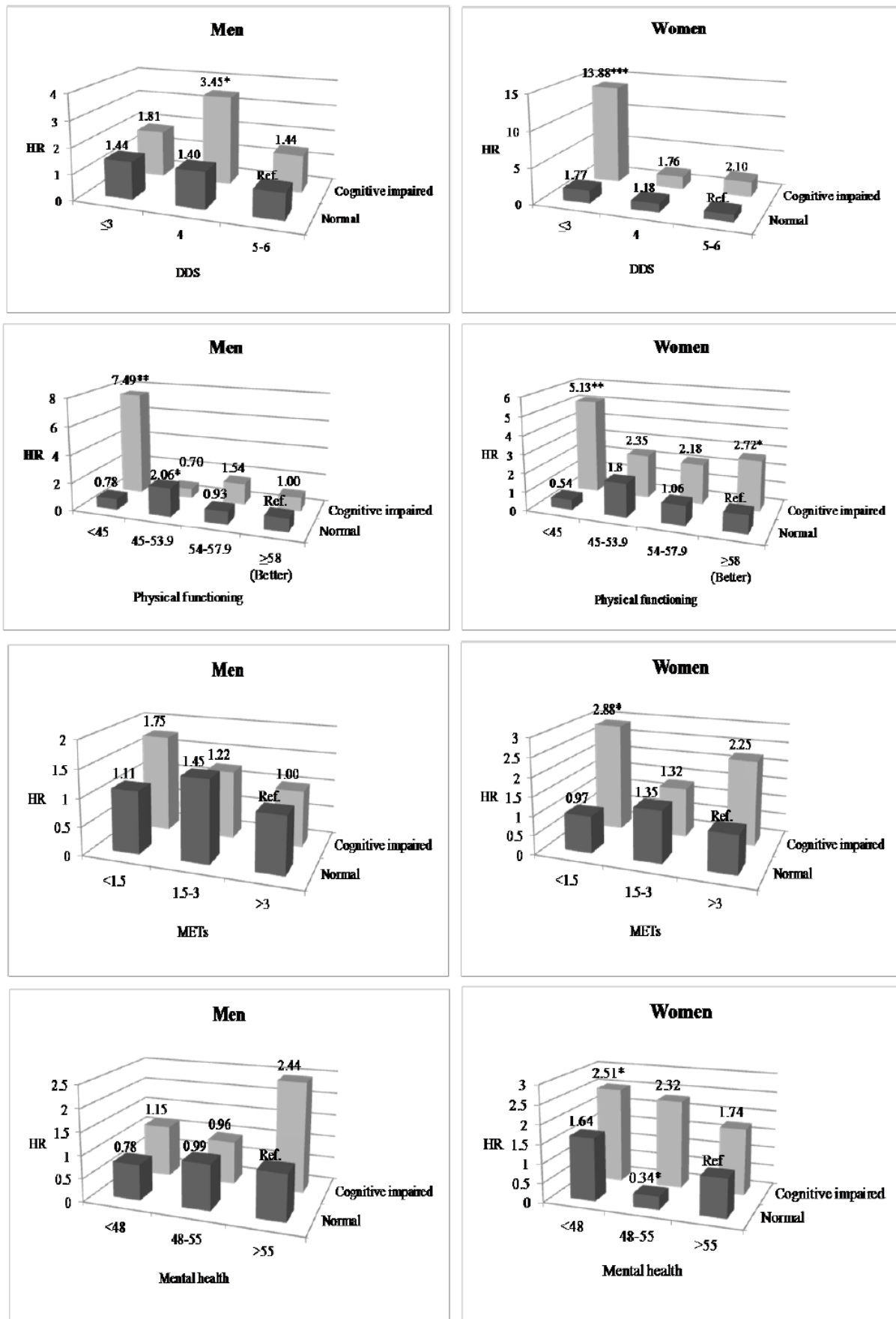


Figure 3. Joint hazard ratios (HRs) for developing diabetes in elder Taiwanese after an 8-year follow-up in accordance with cognitive function and in relation to dietary diversity scores (DDS), physical function and metabolic equivalents (METs). The model has been adjusted for gender, age, education, ethnicity, alcohol drinking, and smoking. Significance is shown by * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. The p value for interaction for cognitive status and DDS in men and women are 0.5 and 0.004; for cognitive status and METs in men and women are 0.7 and 0.03; for cognitive status and physical function in men and women are 0.2 and 0.07, for cognitive status and mental health are 0.7 and 0.04, respectively.

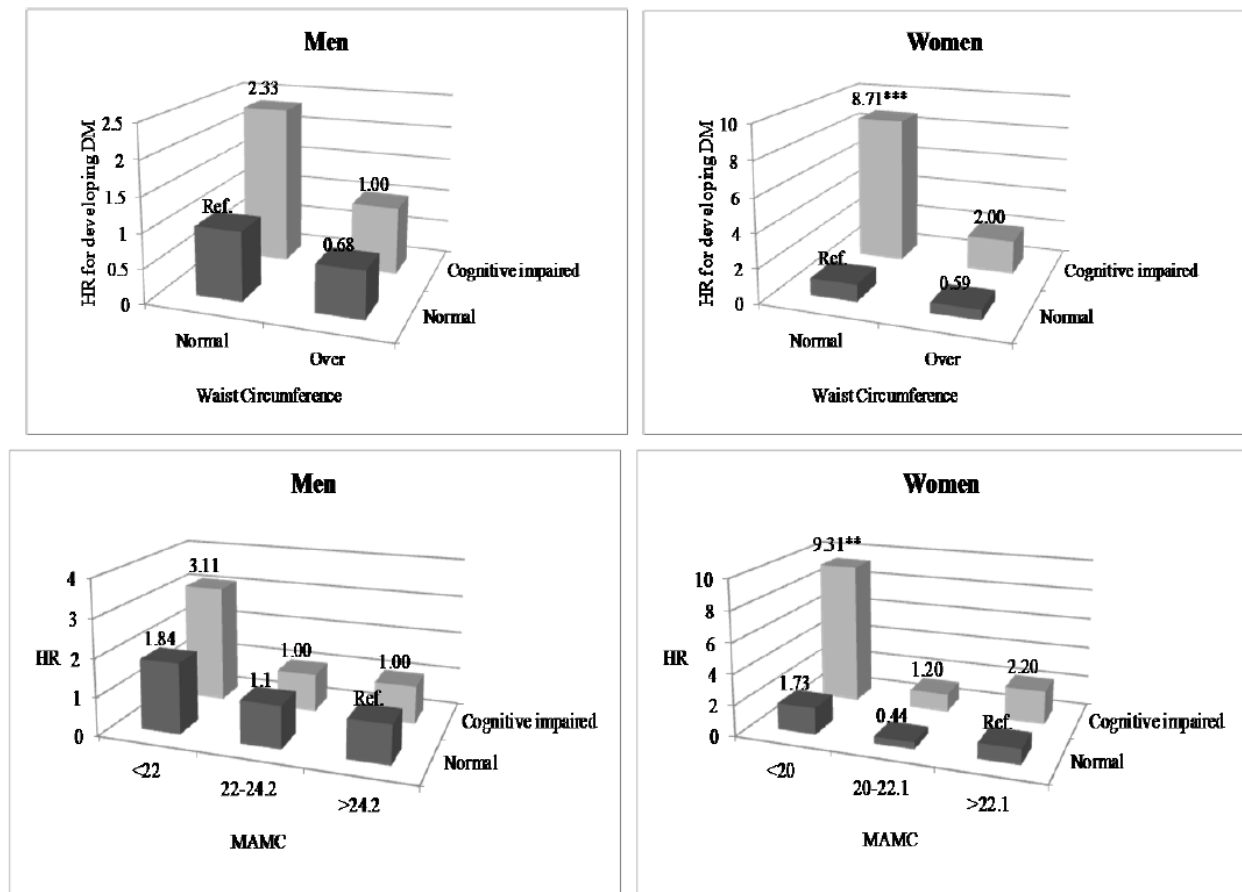


Figure 4. Joint hazard ratios (HRs) for developing diabetes in elder Taiwanese after a 8-year follow-up in accordance with cognitive function and in relation to waist circumference (WC) and Mid-arm muscle circumference (MAMC). The model has been adjusted for gender, age, education, ethnicity, alcohol drinking, and smoking. Significance is shown by ** $p < 0.01$, *** $p < 0.001$. The P value for interaction for cognitive status and WC in men and women are 0.14 and 0.02; for cognitive status and MAMC are 0.2 and 0.002 respectively.

HRs (95% CIs) are, respectively 8.71 (2.67-28.4) and 9.31 (2.58-33.6) for normal WC and the least muscle mass.

DISCUSSION

Cognitive impairment as an antecedent of diabetes

The association between cognitive impairment and diabetes is well-established, although most of the evidence points to hyperglycemia or diabetes as a risk factor for cognitive impairment or dementia.⁵ What we have found is that cognitive impairment can antedate and constitute a risk factor for T2DM. This means that cognitive function may be part of a vicious cycle in the progression of diabetes and its sequelae. It is possible that the risk of diabetes operates across the SPMSQ range which we have not evaluated. Nevertheless, it maybe of clinical and public health importance to consider lesser degrees of cognitive impairment in relation to risk of diabetes.

Gender, being indigenous and joint effects

Population studies of cognitive impairment vary in gender equivalence or dominance of prevalence.³⁵⁻³⁷ A study of elderly Taiwanese in 1990 reported higher prevalences among women than men.³⁸ There are consistent recognized differences in the type of cognitive ability, however, with men better in spatial and number cognition and women in word fluency.^{35,36} In our diabetes-free baseline population, prevalence was greater among women. There

is a gender difference in the risk of incident T2DM when there is cognitive impairment, with an adjusted impact of 2.4-fold in women and no significant impact in men. This raises questions as to the nature of this susceptibility in women. The risk is seen in non-indigenous rather than indigenous women so that ethnicity may play a role. However, we are uncertain as to why there appears to be less susceptibility to diabetes with cognitive impairment among indigenous women, especially since the study design over-sampled minority groups making false negativity less likely. It is noteworthy that the major Taiwanese indigenous communities, the Ami, are matriarchal and matrilineal and this societal strength may play a role.³⁹

The gender effect in those who are dominantly Han Chinese women is amplified, as judged by significant joint effects, by poor dietary quality (assessed by DDS), limited physical function and activity, mental health difficulties and the body compositional factors of less abdominal fatness (WC) and sarcopenia (MAMC<22). These findings may point to the mechanisms involved.

Mechanisms for cognitive impairment as a risk factor for diabetes

Cognitive impairment is associated with a number of phenomena which themselves might contribute to an apparent actual biological basis for its association with diabetes. Chief among these may be socio-cultural,³³ mental stress,¹² perceived health problems or illness cognition.⁴⁰

Notwithstanding a well-established National Health Insurance scheme in Taiwan, equity and poverty have been found to be ongoing concerns in the recognition and management of diabetes.⁴¹ Among elderly Taiwanese, education, ethnicity and perceived financial status were less satisfactory in the cognitively impaired than those not. However, adjustments for these in all joint effect models did not alter the gender differences or associations with antecedent cognitive impairment and diabetes.

With cognitive impairment as a risk factor for diabetes in women of dominantly Han Chinese ancestry, it is conceivable that there is a shared underlying basis for the two health problems. Both have their pre-clinical counterparts, moderate cognitive impairment and pre-diabetes or the metabolic syndrome.

Insulin resistance is a candidate for an underlying pathogenesis as it is not only a feature of pre-diabetes, but has been associated with cognitive impairment.⁴² These observations might be explained by impaired energy regulation (IER) where the plane of energy nutrition or energy throughput might be sufficiently low in some elderly women as to compromise dietary quality.⁴³ This problem of energy regulation may be apparent in diabetes dementia given the favorable associations with metformin with its effects on AMP kinase involved in cellular bioenergetics.⁵ However, a gender difference has not been reported with this association, albeit for diabetes, metformin and cancer⁴⁴ where the energy dysregulatory hepatocellular and colorectal cancers behave differently. Although not significantly conjoint in the present study, poor PF is strongly associated with incident diabetes, as it is in women. Low PF also conjointly with underweight increases the mortality risk in men and women in this elderly Taiwanese population¹⁷ which emphasizes the adverse overall health consequences of impaired energy regulation in the elderly.^{43,44}

The more detailed pathogenesis of cognitive impairment and diabetes might be shared through amyloid deposition in brain and pancreatic islets with their beta cells.⁴⁵ Evidence for type 3 brain diabetes makes a similar case.⁴⁶

Limitations

Diagnostic rates may have been higher in women than in men because of differences in health-seeking behavior.⁴⁰ In this case, the observed gender differences might not have been so great. However, we have also considered the question of gender discrimination in the Taiwanese health care system and show how it is probably not a major factor in regard to the metabolic syndrome and cardiovascular disease where substantial cost differences are nevertheless incurred by gender.⁴⁷

It is possible that we have not taken into account all possible confounders in our exploration of the associations of antecedent cognitive impairment with T2DM. Thus, these associations may be over-stated, although they have been accentuated in the conjoint models and the resultant relative risks are generally large. We have recorded all 8 dimensions of SF-36 and studied 3 of them (physical functioning, mental health and perceived health status) as covariates. We considered that those omitted would be largely covered by the socio-demographic vari-

ables available to us and included in any case, but acknowledge that a clearer picture of cognitive impairment as a risk for diabetes might emerge from the inclusion of each and every SF-36 dimension.

Finally, it is likely that sub-clinical phenomena which we have not ascertained may clarify what presently seems a possible sequential set of events, with cognition preceding T2DM. This is especially so since, separately, we know that the reverse sequence occurs⁵.

Implications

It is of interest to consider the implications of the present findings in light of trends in T2DM prevalence and incidence in Taiwan.⁴⁸ In later life, this may be relevant even for minor degrees of cognitive impairment. While overall adult prevalence has been increasing, increased incidence is located principally among young men aged 20-40 years. Our study is of elders ≥ 65 years where incidence is relatively stable and similar for men and women from 1999-2004, at about 18 per 1000 person-years. It would be useful to establish whether interruption of the cognitive function-diabetes association could decrease the burden of both health problems in later life. Likely candidates for such a strategy include efforts to encourage optimal neuronal energy regulation through enhanced physical function and activity, where energy needs are met with a nutritious diet as judged by its diversity and the emphasis on body compositional health is maintenance of skeletal mass and avoidance of sarcopenia. Although these findings apply to women rather than men in our study, for reasons of general and public health, the same approaches are relevant to men. Moreover, since it is known that insulin resistance may precede both cognitive impairment and diabetes, these strategic steps may abort a shared underlying pathogenesis.

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AUTHOR DISCLOSURES

No author has a conflict of interest in regard to this paper.

REFERENCES

1. Cowie CC, Rust KF, Ford ES, Eberhardt MS, Byrd-Holt DD, Li C et al. Full accounting of diabetes and pre-diabetes in the U.S. population in 1988-1994 and 2005-2006. *Diabetes Care*. 2009;32:287-94. doi: 10.2337/dc08-1296
2. Di Carlo A, Baldereschi M, Amaducci L, Maggi S, Grigoletto F, Scarlato G et al. Cognitive impairment without dementia in older people: prevalence, vascular risk factors, impact on disability. The Italian Longitudinal Study on Aging. *J Am Geriatr Soc*. 2000;48:775-82.
3. Croxson SCM, Jagger C. Diabetes and cognitive impairment - a community-based study of elderly subjects. *Age Ageing*. 1995;24:421-4. doi: 10.1093/ageing/24.5.421
4. Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes--systematic overview of prospective observational studies. *Diabetologia*. 2005;48:2460-9. doi: 10.1007/s00125-005-0023-4
5. Hsu CC, Wahlqvist ML, Lee MS, Tsai HN. Incidence of

- dementia is increased in type 2 diabetes and reduced by the use of sulfonylureas and metformin. *J Alzheimers Dis.* 2011; 24:485-93. doi: 10.3233/JAD-2011-101524
6. Wahlqvist ML, Lee MS, Chuang SY, Hsu CC, Tsai HN, Yu SH et al. Increased risk of affective disorders in type 2 diabetes is minimized by sulfonylurea and metformin combination: a population-based cohort study. *BMC Med.* 10:150. doi: 10.1186/1741-7015-10-150
 7. Biessels GJ, Deary IJ, Ryan CM. Cognition and diabetes: a lifespan perspective. *Lancet Neurol.* 2008;7:184-90. doi: 10.1016/S1474-4422(08)70021-8
 8. Luchsinger JA. Type 2 diabetes and cognitive impairment: linking mechanisms. *J Alzheimers Dis.* 2012;30:S185-S198. doi: 10.3233/JAD-2012-111433
 9. Wahlqvist ML, Lee MS, Hsu CC, Chuang SY, Lee JT, Tsai HN. Metformin-inclusive sulfonylurea therapy reduces the risk of Parkinson's disease occurring with Type 2 diabetes in a Taiwanese population cohort. *Parkinsonism Relat Disord.* 2012;18:753-8. doi: 10.1016/j.parkreldis.2012.03.010
 10. Pan A, Lucas M, Sun Q, van Dam RM, Franco OH, Manson JE et al. Bidirectional association between depression and type 2 diabetes mellitus in women. *Arch Intern Med.* 2012;170:1884-91. doi: 10.1001/archinternmed.2010.356
 11. Berthoud HR, Morrison C. The brain, appetite, and obesity. *Ann Rev Psychol.* 2008;59:55-92. doi: 10.1146/annurev.psych.59.103006.093551
 12. Bjorntorp P. Metabolic implications of body-fat distribution. *Diabetes Care.* 1991;14:1132-43. doi: 10.2337/diacare.14.12.1132
 13. Lupien SJ, Maheu F, Tu M, Fiocco A, Schramek TE. The effects of stress and stress hormones on human cognition: Implications for the field of brain and cognition. *Brain Cogn.* 2007;65:209-37. doi: 10.1016/j.bandc.2007.02.007
 14. Pan WH, Hung YT, Shaw NS, Lin W, Lee SD, Chiu CF et al. Elderly Nutrition and Health Survey in Taiwan (1999-2000): research design, methodology and content. *Asia Pac J Clin Nutr.* 2005;14:203-10.
 15. Chen RCY, Chang YH, Lee MS, Wahlqvist ML. Dietary quality may enhance survival related to cognitive impairment in Taiwanese elderly. *Food Nutr Res.* 2011;55:7387. doi: 10.3402/fnr.v55i0.7387
 16. Lee MS, Huang YC, Su HH, Lee MZ, Wahlqvist ML. A simple food quality index predicts mortality in elderly Taiwanese. *J Nutr Health Aging.* 2011;15:815-21. doi: 10.1007/s12603-011-0081-x
 17. Lee MS, Chen RCY, Chang YH, Huang YC, Wahlqvist ML. Physical function mitigates the adverse effects of being thin on mortality in a free-living older taiwanese cohort. *J Nutr Health Aging.* 2012;16:776-83. doi: 10.1007/s12603-012-0379-3
 18. Lu JF, Tseng HM, Tsai YJ. Assessment of health-related quality of life in Taiwan (I): development and psychometric testing of SF-36 Taiwan version. *Taiwan J Public Health.* 2003;22:501-11.
 19. Tu SH, Chen C, Hsieh YT, Chang HY, Yeh CJ, Lin YC et al. Design and sample characteristics of the 2005-2008 Nutrition and Health Survey in Taiwan. *Asia Pac J Clin Nutr.* 2011;20:225-37.
 20. American Diabetes Association (ADA). Diagnosing Diabetes and Learning About Prediabetes. [Cited 2013/08/16]; Available from: <http://www.diabetes.org/diabetes-basics/diagnosis/?loc=DropDownDB-diagnosis>
 21. Gibson RS. Nutritional assessment. A laboratory manual. New York: Oxford University Press; 1933.
 22. World Health Organization, International Association for the study of obesity & international obesity task force. The Asia-Pacific Perspective: Redefining Obesity and Its Treatment. Sydney: Health communications; 2000
 23. Wen CP, Cheng DTY, Tsai SP, Chan HT, Hsu HL, Hsu CC et al. Are Asians at greater mortality risks for being overweight than Caucasians? Redefining obesity for Asians. *Public Health Nutr.* 2009;12:497-506. doi: 10.1017/S1368980008002802
 24. Ware J. How to Score the Revised MOS Short-Form Health Scale (SF-36®). Boston, MA: The Health Institute, New England Medical Center Hospitals; 1988.
 25. Ware J. KM, Keller S. SF-36 Physical and mental health summary scales: A user's manual. Quality Metric Inc.; 1997.
 26. Wahlqvist ML, Lo CS, Myers KA. Food variety is associated with less macrovascular disease in those with type 2 diabetes and their healthy controls. *J Am Coll Nutr.* 1989;8:515-23.
 27. Sayer AA, Dennison EM, Syddall HE, Gilbody HJ, Phillips DI, Cooper C. Type 2 diabetes, muscle strength, and impaired physical function: the tip of the iceberg? *Diabetes Care.* 2005;28:2541-2. doi: 10.2337/diacare.28.10.2541
 28. Tudor-Locke C, Schuna JM, Jr. Steps to preventing type 2 diabetes: exercise, walk more, or sit less? *Front Endocrinol.* 2012;3:142. doi: 10.3389/fendo.2012.00142
 29. Narayan KM, Boyle JP, Thompson TJ, Gregg EW, Williamson DF. Effect of BMI on lifetime risk for diabetes in the U.S. *Diabetes Care.* 2007;30:1562-6. doi: 10.2337/dc06-2544
 30. de Hollander EL, Bemelmans WJE, Boshuizen HC, Friedrich N, Wallaschofski H, Guallar-Castillon P et al. The association between waist circumference and risk of mortality considering body mass index in 65-to 74-year-olds: a meta-analysis of 29 cohorts involving more than 58,000 elderly persons. *Int J Epidemiol.* 2012;41:805-17. doi: 10.1093/ije/dys008
 31. Langenberg C, Sharp SJ, Schulze MB, Rolandsson O, Overvad K, Forouhi NG et al. Long-term risk of incident type 2 diabetes and measures of overall and regional obesity: the EPIC-Interact case-cohort study. *Plos Med.* 2012;9:e1001230. doi: 10.1371/journal.pmed.1001230
 32. Chen HD, Shaw CK, Tseng WP, Chen HI, Lee ML. Prevalence of diabetes mellitus and impaired glucose tolerance in Aborigines and Chinese in eastern Taiwan. *Diabetes Res Clin Pract.* 1997;38:199-205. doi: 10.1016/S0168-8227(97)00104-6
 33. Wen CP, Tsai SP, Shih YT, Chung WS. Bridging the gap in life expectancy of the aborigines in Taiwan. *Int J Epidemiol.* 2004;33:320-7. doi: 10.1093/ije/dyh009
 34. Chang CH, Shau WY, Jiang YD, Li HY, Chang TJ, Sheu WHH et al. Type 2 diabetes prevalence and incidence among adults in Taiwan during 1999-2004: a national health insurance data set study. *Diabet Med.* 2010;27:636-43. doi: 10.1111/j.1464-5491.2010.03007.x
 35. Wiroth JB, Bermon S, Andrei S, Dalloz E, Hebuterne X, Dolisi C. Effects of oral creatine supplementation on maximal pedalling performance in older adults. *Eur J Appl Physiol.* 2001;84:533-9. doi: 10.1007/s004210000370
 36. Maitland SB, Intrieri RC, Schaie KW, Willis SL. Gender differences and changes in cognitive abilities across the adult life span. *Aging Neuropsychol Cogn.* 2000;7:32-53. doi: 10.1076/anec.7.1.32.807
 37. Busse A, Bischof J, Riedel-Heller SG, Angermeyer MC. Mild cognitive impairment: prevalence and incidence according to different diagnostic criteria - Results of the Leipzig Longitudinal Study of the Aged (LEILA75+). *Br J Psychiatry.* 2003;182:449-54. doi: 10.1192/bjp.182.5.449
 38. Yeh EK, Chang LY. Lifetime prevalence of cognitive impairment by Chinese-modified NIMH diagnostic interview schedule among the elderly in Taiwan

- communities. *J Neurolinguistics*. 1990;5:83-104. doi: 10.1016/0911-6044(90)90033-U
39. Council of Indigenous Peoples, Executive Yuan, Taiwan. [Cited 2013/08/16]; Available from: [http://www.tacp.gov.tw/tacpeng/home02_3.aspx?ID=\\$3051&IDK=2&EXEC=L](http://www.tacp.gov.tw/tacpeng/home02_3.aspx?ID=$3051&IDK=2&EXEC=L).
40. Keogh KM, White P, Smith SM, McGilloway S, O'Dowd T, Gibney J. Changing illness perceptions in patients with poorly controlled type 2 diabetes, a randomised controlled trial of a family-based intervention: protocol and pilot study. *BMC Fam Pract*. 2007;8:36. doi: 10.1186/1471-2296-8-36
41. Hsu CC, Lee CH, Wahlqvist ML, Huang HL, Chang HY, Chen L et al. Poverty increases type 2 diabetes incidence and inequality of care despite universal health coverage. *Diabetes Care*. 2012;35:2286-92. doi: 10.2337/dc11-2052
42. Talbot K, Wang HY, Kazi H, Han LY, Bakshi KP, Stucky A et al. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. *J Clin Invest*. 2012; 122:1316-38. doi: 10.1172/JCI59903
43. Wahlqvist ML, Chang HY, Chen CC, Hsu CC, Chang WC, Wang WS et al. Is impaired energy regulation the core of the metabolic syndrome in various ethnic groups of the USA and Taiwan? *BMC Endocr Disord*. 2012;10:11. doi: 10.1186/1472-6823-10-11
44. Lee MS, Hsu CC, Wahlqvist ML, Tsai HN, Chang YH, Huang YC. Type 2 diabetes increases and metformin reduces total, colorectal, liver and pancreatic cancer incidences in Taiwanese: a representative population prospective cohort study of 800,000 individuals. *BMC Cancer*. 2011;11:20. doi: 10.1186/1471-2407-11-20
45. Janson J, Laedtke T, Parisi JE, O'Brien P, Petersen RC, Butler PC. Increased risk of type 2 diabetes in Alzheimer disease. *Diabetes*. 2004;53:474-81. doi: 10.2337/diabetes.53.2.474
46. de la Monte SM, Wands JR. Alzheimer's disease is type 3 diabetes – evidence reviewed. *J Diabetes Sci Technol*. 2008; 2:1101-13.
47. Chang YH, Chen RCY, Lee MS, Wahlqvist ML. Increased medical costs in elders with the metabolic syndrome are most evident with hospitalization of men. *Gend Med*. 2012; 9:348-60. doi: 10.1016/j.genm.2012.08.005
48. Chang CH, Shau WY, Jiang YD, Li HY, Chang TJ, Sheu WH, Kwok CF, Ho LT, Chuang LM. Type 2 diabetes prevalence and incidence among adults in Taiwan during 1999-2004: a national health insurance data set study. *Diabet Med*. 2010;27:636-43. doi: 10.1111/j.1464-5491.2010.03007.x

Original Article

Cognitive impairment and limited dietary diversity or physical inactivity are conjoint precursors of incident diabetes more so in elderly women than men

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認知功能障礙伴隨單調飲食或缺乏運動是老年女性而非男性罹患糖尿病的前導因子

已有研究發現患有糖尿病的老人易發生認知功能障礙，對於患有認知功能障礙的老人是否更易發生糖尿病，也就是老人糖尿病和認知功能障礙發生是否存在雙向性影響，目前不可知。本研究的目的為觀察患有認知功能障礙的老人是否更容易發生糖尿病。以參與 1999-2000 年臺灣老人營養和健康調查中 1493 位年齡超過 65 歲，且沒有糖尿病的老人為研究對象，追蹤 8 年，研究糖尿病發生率和認知功能的關係。認知功能障礙和糖尿病的發生率以 Cox 比例風險迴歸模型來分析。結果發現有認知功能障礙的女性其糖尿病發生率顯著提高，但在男性中沒有觀察到這樣的結果。以正常認知功能組做為參照組，在校正年齡，性別，種族和個人行為之後，認知功能障礙老年女性二型糖尿病風險比值(HR)為 2.43 (95%信賴區間: 1.27-4.63)，男性為 1.55 (95%信賴區間: 0.48-5.07)。在分別校正年齡，種族，個人行為和經濟狀況，飲食品質，身體活動功能，運動，空腹血糖值，身體質量指數，腰圍及中臂肌圍等可能影響糖尿病發生的變數後，性別差異和風險比顯著性仍然存在。在女性中，上述共變數對糖尿病的發生存在顯著交互作用。飲食品質差及少運動，會增加認知功能障礙老年女性患糖尿病的風險比。

關鍵字：認知功能障礙、第二型糖尿病、飲食、運動、身體組成