DETERMINANTS OF DIABETES MELLITUS TYPE 2 RISK IN RON PHIBOON SUB-DISTRICT, NAKHON SI THAMMARAT PROVINCE, THAILAND

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ABSTRACT:

Background: Diabetes mellitus (DM) is a chronic metabolic disease resulting from diminished insulin production by pancreas (type 1) or the ineffective use of insulin by the body (type 2). Known risk factors for DM, especially DM type 2, include older age, obesity; unbalanced diet, physical inactivity, stress, family history, and genetic polymorphisms. Ron Phiboon district, Nakhon Si Thammarat province locates in the South of Thailand. According to data from provincial health office, the rate of DM per 100,000 people in Nakhon Si Thammarat Province in 2008 was 1150.7, whereas the rate in the same year, as reported by Diabetes clinic of Ron Phiboon hospital, was 1742 compared to 972 in the year 2004. The increased rates of DM patients in that area led to the investigation of DM risk factors, to add more information for DM risk mitigation. Thus, this study focused on investigation of determinants of DM type 2 risk among residents of 3 Moo Ban (villages) of Ron Phiboon sub-district, Nakhon Si Thammarat province, Thailand.

Methods: This unmatched case-control study aimed to compare the socioeconomic patterns between villagers with DM Type 2 (Cases, N=185) and those who had not been diagnosed with DM (controls, N=200). The data used were based on previous community-based studies in 2000 and 2008. The technique of Multiple Imputation (MI), with the Predictive Mean Matching (PMM, an imputation method used to prevent negative value after MI) was used to impute missing values for independent variables. The stepwise modelling was constructed to investigate the influence of socio-economic background and lifestyles such as sources of water used on DM risk. For fully imputed data set of cases and unmatched controls, multiple logistic regression was used to assess associations.

Results: BMI (*p*-value <0.001), age (*p*-value 0.006), and history of sibling illness (*p*-value 0.024) were statistically significantly associated with increased risk of DM type 2 (*p*-value <0.05), whereas having motorcar (representing better economic status, *p*-value 0.029), was associated with lower DM type 2 risk. Exercise was associated with increased DM type 2 risk, though not statistically significantly.

Conclusions: Our findings on socioeconomic information in this unmatched case control study confirm that BMI, age, and history of illness of sibling were the determinants for increased DM type 2 risk in the study area. Having better economic status was found to be associated with lower DM type 2 risk. These findings could help policy makers to manage DM type 2 risk factors in the area of Ron Phiboon sub-district, Ron Phiboon district, Nakhon Si Thammarat Province, Thailand.

Keywords: Determinants; Diabetes risk; Diabetes mellitus type 2; Thailand

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease resulting from impaired insulin production

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by the pancreas (type 1) or the ineffective use of insulin by the body (type 2). It causes major health problems both global and national. The persistency of elevated blood sugar might lead to many severe complications. DM type 2 is the most common form, normally found in adults aged over 30 years. Since the onset is a slow process and the symptoms develop slowly, rapid diagnosis is difficult. Its known risk factors include age, family history, genetic, high blood pressure, central-adiposity, lack of exercise, obesity and diets [1]. Apart from genetics, life style, occupation, some toxicants in environment including arsenic might be responsible for increased prevalence of DM type 2 worldwide [1]. According to survey of Thai population on burden of diseases and its risk factors of the year 1999 and 2004 by the working group on burden of disease and injuries among Thais, the Thai Ministry of Public Health (information from published announcement), the DALYs (Disability Adjusted Life Years) caused by DM of the year 2004 was 1.7 years per 100,000 persons among male and 2.7 years per 100,000 persons among female. It was reported that the estimated national prevalence of diabetes in Thai adults (aged ≥35 years) was 9.6 % (2.4 million people), which included 4.8% previously diagnosed and 4.8 % newly diagnosed [2]. In year 2008, according to data from Nakhon Si Thammarat Provincial Health Office, the reported number of DM patients (both genders) was 17412 (from total population of 1,513,163 people), and rate of DM per 100,000 people was 1150.7. The residents of Ron Phiboon sub-district, Ron Phiboon district, Nakhon Si Thammarat Province, had lived in this area for three generations. As reported by diabetes clinic of Ron Phiboon hospital, the rate of DM (both genders) per 100,000 people of Ron Phiboon sub-district in year 2004 and year 2008 were 972 and 1742 respectively. An increased rate of nearly 2 fold of DM per 100,000 within 4 years led us to investigate the determinants of DM type 2 risk in the area. Among 16 Moo Ban of Ron Phiboon sub-district, accumulated number and percentage of DM patients during 1988-2008 in Moo 12, Moo 2 and Moo 13 ranked first, third, and fifth respectively, whereas these 3 Moo Ban had history of high arsenic contamination in environment as well. Moo 2 is more rural than Moo 12 and 13 (located in municipal area). While the majority of residents in Moo 12 and Moo 13 could access to municipal tap water, those who lived in Moo 2 were not. Thus, this study focused on investigation of determinants of DM type 2 risk among residents of 3 Moo Ban of Ron Phiboon sub-district, Nakhon Si Thammarat province, Thailand.

METHODS

Unmatched case-control study to compare the socio-economic pattern between villagers with DM type 2 and those who had not been diagnosed with DM type 2, in the population of Ron Phiboon sub-district's above-mentioned three Moo Ban was conducted. Various data were collected in the year 2000 and 2008. In the current study, we collected data from 185 cases (C), and 200 unmatched controls (UMC). Cases were those who had been diagnosed with diabetes type 2. During year 2000 to 2013, new patients were diagnosed according to specified criteria of Ron Phiboon hospital, WHO, and old patients were characterized by reviewing the outpatient cards (OPD) at the Ron Phiboon hospital. They were those who had lived in Moo 2, 12 and 13 of Ron Phiboon sub-district, Ron Phiboon district, Nakhon Si Thammarat Province for more than one year, male or female, at least 35 years old. For control group, they were those who did not have DM type 2 (using the same diagnostic criteria as the case group), male or female, had lived in the same area as case group for more than one year, and at least 35 years old. They were selected randomly as a subsample of combined population of the 3 Moo ban (Moo 2, 12, 13) of Ron Phiboon sub -district. Thus, the controls were intended to be representative of the overall study population.

Secondary data from previous two communities based studies in 2000 and 2008 were used. For all needed socioeconomic information and sources of water that individual used for consumption, questionnaire (year 2000) and worksheet for health risk screening with additional worksheet for water collection (year 2008) with face to face interviews were used in data collection. Information on melanosis or hyperkeratosis (as a potential marker of water arsenic exposure) was obtained after skin examination of individuals by specially trained nurse at the time of interviewing. Information from those two years' studies was combined into a single data file for further analysis.

Among others, data of independent variables such as gender, age, BMI, having exercise, residency in different Moo Ban (Moo 2, 12, 13) and length of residence (years), history of illness of parents and siblings, smoking, drinking, observation of melanosis or hyperkeratosis, married status,

Table 1 Selected characteristics among case and control groups

Variables	Case group N=185	Control group N=200	Total N=385
Male; Count (%)	61 (33)	78 (39)	139
Age as of year 2008; Mean (SE)	58.5 (0.828)	52.8 (0.932)	-
BMI year 2008; Mean (SE)	25.3 (0.320)	22.4 (0.260)	-
Doing exercise at least 30 minute/time and > 3 times/week; count (%)	81 (43.7)	51 (25.4)	132
Having history of illness of parent; count (%)	83 (44.9)	42 (21)	125
Having history of illness of sibling; count (%)	88 (47.8)	29 (14.5)	117
Ever smoking; count (%)	74 (39.9)	39 (19.7)	113
Ever drinking; count (%)	81 (43.8)	37 (18.6)	118
Melanosis or hyperkeratosis is observed; count (%)	106 (57.3)	115 (57.5)	221
Actively married; count (%)	96 (51.8)	93 (46.7)	189
Have basic and higher education; count (%)	67 (36.4)	86 (43.2)	153
Length of resident (year) in Ron Phiboon sub-district; Mean (SE)	37.4 (13.69)	38.4 (14.85)	-
Being farmer; count (%)	19 (10.3)	15 (7.5)	34
Being government employer; count (%)	18 (9.7)	12 (6)	30
Having and driving car motor; count (%)	116 (62.7)	170 (85)	286

Note: SE = Standard Error (For continuous variable). Because the independent t-test in the MI method does not give the Standard deviation (SD), SE is used instead.

Table 2 Descriptive information on evidence of types of water used in case and control groups

Variables	Case group N=185	Control group N=200	Total N=385
Use of municipal tap waterY2000; count (%)	102 (55.4)	95 (47.5)	197 (51.2)
Use of village tap water Y2000; count (%)	79 (42.8)	89 (44.4)	168 (43.6)
Use of bottle water Y2000; count (%)	68 (36.9)	81 (40.4)	149 (38.7)
Use of well water Y2000; count (%)	97 (52.4)	122 (61.1)	219 (56.9)
Use of rain water Y2000; count (%)	127 (68.4)	136 (68.2)	263 (68.3)
Use of municipal tap waterY2008; count (%)	93 (50.5)	94 (46.8)	187 (48.6)
Use of village tap water Y2008; count (%)	99 (53.4)	129 (64.5)	228 (59.2)
Use of bottle water Y2008; count (%)	63 (34.2)	77 (38.5)	140 (36.4)
Use of well water Y2008; count (%)	74 (39.8)	81 (40.3)	155 (40.3)
Use of rain water Y2008; count (%)	78 (42.3)	117 (58.3)	195 (50.6)

education, occupation (being farmer, being government officer or own business), and having a motorcar (representing economic status) were scrutinized for association with DM type 2 in the area. Having exercise in this study means those who have exercise at least 30 minutes per time and 3 times per week. We classified having either diabetes (DM), hypertension (HT), gout, chronic renal failure (CRF), myocardial Infarction (MI), stroke, chronic obstruction pulmonary disease (COPD) and paralysis or myocardial ischemia as having history of illness of both parent and sibling categories, though some of this disease are not quite relate to DM. This is because of limitation of data availability since the questionnaire that we used as source document was aimed to screen health risks among population for national survey purposes, not specifically for screening of DM frequency. Variables indicating evidence of use of 5 types of water (municipal tap water, village tap water, bottled water, well water and rain water were constructed by combining evidence of use of that type of water either from questionnaire responses regarding water source or from the availability of arsenic concentration in that type of water for individual subjects.

For data analysis, Multiple Imputation (MI), a computational statistical method was used to impute missing value for independent variables. There are 3 steps for MI analysis; first, formulation of imputation model and a series of imputed dataset are then created. Second, each imputed dataset is analyzed separately. And third, a single set of estimates are generated from the pooled imputed datasets. The MI estimate of the standard error (S.E) of a parameter is square root of within imputation variance plus between imputation variance. Within imputation variance is the average of variances

across imputations and between imputations variance is function of variance of parameters estimated across the imputed datasets and number of imputation. Thus, uncertainty in the imputed values is accounted for by combining the results across imputations. For fully imputed data set of cases and unmatched controls, multiple logistic regression was employed for association analysis whereby a significant association is identified when *p*-value is <0.05. To prevent negative value after MI of scale variables, the Predictive Mean Matching (PMM) (as imputation method in method subcommand of MI, SPSS version 22.0) was used [3]. To reduce uncertainty, variables that have percentage of missing value more than 80% were not imputed or included in the model.

Among selected variables, we first constructed a full analysis model (model 1) comprising following input variables: being male, age as of year 2008, BMI year 2008, exercise, living in different Moo Ban (Moo 2 12 13; Moo2 as reference), having history of illness of parent as well as of sibling, smoking, drinking, having symptom of either melanosis or hyperkeratosis, married status, education level, year of residency in Ron PhiBoon, being farmer and being Government official or having own business (being labors and others as reference), and having motorcar (represent a better economic status), evidence of use of water types for consumption in year 2008 and year 2000. We then, constructed a number of consecutive intermediate models (model 2 to model 4) to investigate the interaction among those variables whereby a cutoff point for *p*-value of 0.200 was used for selection of input variables (Table 3).

RESULTS

Selected characteristics of case and unmatched control groups are presented in Table 1, whereby mean and standard error (SE) of age as year 2008, Body Mass Index (BMI) as of the year 2008, Length of residence (years) in Ron Phiboon sub-district were 58.5 (.828), 25.3 (.32), 37.3 (13.69) in case group, and 52.8 (.932), 22.4 (.26), 38.4 (14.85) in control group, respectively. The number (%) of individual who: Being male; Doing exercise; Having history of illness of parent; Having history of illness of sibling; Ever smoking; Ever drinking; Melanosis or hyperkeratosis (as a metric of potential water arsenic exposure) is observed; Actively married; Have basic and higher education; Being farmer; Being government employer; Having and driving a motorcar of case and control groups are described in Table1 as well.

All cases were patients of DM clinic at Ron Phiboon Hospital who had residency in Moo 2, Moo 12 and Moo 13. The numbers of diagnosed cases were updated as of year 2013. Table 2 presents frequencies of use of the different water types (municipal tap water, village tap water, bottled water, well water and rain water) used for consumption in year 2008 and year 2000 in case and control groups. For the year 2000, those usage percentages of municipal tap water, village tap water, bottled water, well water, rain water are 55.4, 42.8, 36.9, 52.4, 68.4 in case group and 47.5, 44.4, 40.4, 61.1, 68.2 in control group respectively. In the year 2008, percentage of use of municipal tap water, village tap water, bottled water, well water, rain water are 50.5, 53.4, 34.2, 39.8, 42.3 in case group and 46.8, 64.5, 38.5, 40.3, 58.3 in control groups. Rain, well and municipal tap water are top three ranking in year 2000; whereas village tap water, rain water, and municipal tap water are the top three ranking in the year 2008.

Comparison results of association analysis after MI of 4 models comprise of selected input variables are shown in Table 3. Those variables are grouped into 2, a group of established risk factors and a group of potential risk factors for DM type 2. In the final model (model 4), the *p*-values (OR) of those adjusted variables of age as of year 2008, BMI year 2008, exercise, having history of illness of parent, history of illness of sibling, drinking, having motorcar (represent a better economic status), and use of rain water in 2008 are 0.006 (1.035), <0.001 (1.194), 0.095 (2.089), 0.132 (2.348), 0.024 (3.668), 0.073 (3.085), 0.029 (0.388), and 0.099 (0.478) respectively. A cutoff point for *p*-value of 0.200 was used for selection of input variables in consecutively constructed model 2, 3 and 4. Thus, all blank cells in Table 3 represent excluded variables' results due to their *p*-values being above the cutoff point.

DISCUSSION AND CONCLUSION

The findings regarding sociodemographic information of this unmatched case control study confirm that older age, BMI, having history of illness of sibling were associated with higher DM type 2 risk, whereas having motorcar, representing better economic status, is associated with lower DM type 2 risk in the study area. Our analysis suggested no convincing association of water arsenic with diabetes risk. Further research is needed on this topic.

Table 3 Results after multiple imputation of 4 consecutively constructed models analysis for different input variables for DM type 2 risk association.

Input variables	Model 1		Model 2		Model 3		Model 4	
	Odds Ratio	*p*-value	Odds Ratio	*p*-value	Odds Ratio	*p*-value	Odds Ratio	*p*-value
Established risk factors for DM type 2								
Male	0.596	0.183	0.607	0.122	0.666	0.207		
Age As of year 2008	1.035	0.011	1.032	0.014	1.035	0.008	1.035	0.006
BMI year 2008	1.208	0.001	1.190	<0.001	1.188	<0.001	1.194	<0.001
Exercise	2.227	0.080	2.096	0.095	2.107	0.087	2.089	0.095
Potential risk factors for DM type 2								
Moo12 (Reference=Moo2)	0.853	0.807						
Moo13(Reference=Moo2)	1.059	0.924						
History of illness of parent	2.467	0.173	2.190	0.172	2.275	0.161	2.348	0.132
History of illness of sibling	4.161	0.040	3.673	0.025	3.735	0.024	3.668	0.024
Ever smoke?	2.051	0.194	1.746	0.315				
Ever drink?	2.997	0.169	2.779	0.190	3.543	0.055	3.085	0.073
Having either melanosis or hyperkeratosis?	0.913	0.880						
Married, living with spouse	1.100	0.834						
Higher education?	0.712	0.490						
Length of residence in Ron Phiboon	1.004	0.704						
Being farmer (Reference = Labor and others)	0.662	0.512						
Being Government official or having own business (Reference=Labor and others)	0.727	0.644						
Having motorcar (including motorcycle)	0.395	0.045	0.397	0.040	0.412	0.041	0.388	0.029
Evidence of use of municipal tap water year 2000	1.549	0.539						
Evidence of use of village tap water year 2000	0.931	0.875						
Evidence of use of bottle water year 2000	1.176	0.767						
Evidence of use of well water year 2000	0.782	0.616						
Evidence of use of rain water year 2000	1.007	0.990						
Evidence of use of municipal tap water year 2008	0.804	0.625						
Evidence of use of village tap water year 2008	0.903	0.867						
Evidence of use of bottle water year 2008	0.564	0.248						
Evidence of use of well water year 2008	0.905	0.855						
Evidence of use of rain water year 2008	0.448	0.172	0.469	0.087	0.472	0.102	0.478	0.099

DM is considered a metabolic disease resulting from (1) defects in insulin secretion by pancreatic ß-cells, (2) impairment of insulin action on peripheral tissue namely adipocytes and muscle, and/or (3) an increase in endogenous glucose production by liver [4]. Identified main related factors for insulin resistance are age, sex, central adiposity, genetic, circulating insulin antagonist (hormone, free fatty acid, TNF-α), obesity, lack of physical activity, glucose toxicity and others such as pregnancy, ageing, and drug use [1].

In this study, BMI and older age are found to be associated with increased DM type 2 risk, like others previous epidemiology report worldwide [1, 5, 6]. After the follow-up period of 1499.5 person-years and bi-annually followed 446 non-diabetic residents living 5 days/ week in three villages in Taiwan, age and body mass index were found to be significantly associated with diabetes incidence [7].

Physical inactivity is considered as known risk factor for DM type 2 [1, 6]. We found that exercise is associated with increased DM type 2 risk, though not significant. To evaluate this unexpected finding, we looked at the association of exercise with age, BMI, history of illness of parents and siblings (DM included), and having a motorcar. We found little or no association between exercise and age, BMI, and motorcar. We did see strong positive association between exercise and history of illness in parents or siblings, whereby those who have reported that having parents or siblings illness did exercise more than those who had not. In view of this, it is conceivable that our observed positive association of exercise and DM type 2 risk (data not shown)

could actually be a reflection of reverse causality, whereby knowledge that DM or other chronic illness had occurred in their family, induced participants to increase their exercise levels. Further research is required to ascertain the true relationship between exercise and DM type 2 risk in the study area.

History of illness in siblings was found to be associated with higher DM type 2 risks. Our finding is similar to those reported previously [1, 8]. Though we found that history of illness in sibling is the potential risk factor of DM type 2, the knowledge on linkage between genetic effects and DM type 2 risk is limited. After evaluating effects of gene and socioeconomic characteristics on concentration of toxic metals such as arsenic (As), cadmium (Cd), mercury (Hg) and of essential elements such as Selenium (Se), Zinc (Zn) in blood samples of Australian twin pairs, it was reported that variation in concentration of arsenic and mercury were due mainly to common genetic effect [9]. This group reported that alcohol consumption is significantly associate with increased As, Hg, Pb and Se concentrations, whereas increased years of education associate with decreased As, Hg, Pb concentrations. They also found that genetic effect on essential elements such as Cu, Se, Zn could modulate concentration of toxic effects of other elements. This finding could explain why epidemiological studies of association between heavy metals exposure at low to moderate dose and DM type 2 risk have yielded inconclusive results.

Having motorcar, representing better economic status is found to be strongly associated with lower DM type 2 risk. One possible explanation is that those who have enough income to buy and drive motorcar could access more choices of water source that usually had low arsenic contamination such as rain water, or bottled water (product from outside the study area). However, cautious interpretation is required here, since the finding might be related to other factors such as gender, lifestyles, whereby it was observed that being female did not drive as much of motorcar as male (male; 79%, female; 72%).

For smoking history, we classified never and ever smoking by face to face interview using constructed questionnaire. We did not find association of smoking with DM type 2 risk. A meta-analysis result by J.S. Tsuji et al. that aimed to assess the risk of arsenic at low dose exposure on bladder cancer showed that the summary relative risk estimate (SRRE) of 9 related studies in never smokers were inconsistent with predicted values extrapolated from the high dose exposure from Taiwan's studies and they proposed to examine the risk of arsenic exposure among smokers [10]. In our study, after pursuing different model analysis, we could identify the interaction of drinking and being male, as well as smoking (Table 3; model 2, 3, 4). We found that drinking is marginally associated with increased DM type 2 risk ($p = 0.055$) when keeping male and exclude smoking in analysis model. However, when excluding both male and smoking variables, the association was less strong ($p = 0.073$). It would be useful to find out whether different diet habits among smokers and never smokers could contribute to this outcome result or not.

We did not find association between residency in different Moo Ban (Moo 2: reference, Moo 12, Moo13), length of resident in this area and DM type 2 risk. Our study population spent 38 years, on average, staying in these 3 Moo Ban. We selected Moo 2 as reference group just because its location is not in the municipal area as Moo 12 and 13. Drinking alcohol, skin lesions (having symptom of melanosis or hyperkeratosis), married status, education level, occupation (being farmer, government official/having own business) were not found to be associated with DM type 2 risk either.

We compared water consumption variables indicating evidence of use of 5 types of water (municipal tap water, village tap water, bottle water, well water and rain water. Each one of these set of variables is constructed by combining evidence of use of that type of water from either they said they use it in questionnaire or from the availability of arsenic concentration of that type of water. Among these variables, only use of rain water was associated, indirectly with diabetes risk (OR=0.478, *p*-value=0.099 in the final model).

In a community-based case-control study in Mexico, after adjusting for potential confounding such as sex, age, triglycerides, body mass index, hypertension, family history of DM, and using tertiles distribution of arsenic in urine as cut-off point in the model, Coronado-Gonzalez et al. (2007) reported that the higher risk of DM type 2 were related to age, being female, and the presence of high blood pressure [11].

LIMITATIONS AND UNCERTAINTIES

In this study, some limitations with missing data exist. Inappropriate handling of missing data or

missing data itself may lead to bias and loss of information [12]. Multiple imputation (MI) technique with predictive mean matching (PMM) method attached in SPSS 22.0 (IBM) was used to reduce risk of bias. Special attention had been paid to the selection of control group and confounding factors so that the case-control designed for this study is not a problematic itself.

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