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REVIEW

Metabolically healthy obesity without fatty liver and risk of incident type 2 diabetes: A meta-analysis of prospective cohort studies

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Metabolic syndrome;
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Summary
Objective: A meta-analysis indicated that metabolically healthy obesity (MHO) presents a risk of incident type 2 diabetes, but it has not yet been established whether MHO without fatty liver (w/o FL) also presents a risk of incident diabetes.
Methods: We searched the MEDLINE and Embase databases to identify relevant prospective cohort studies and we supplemented the search with original data from the NAGALA (NAfld in Gifu Area, Longitudinal Analysis) study, defining MHO as a body mass index (BMI) $\geq$25 kg/m^2 plus the presence of non or one of the following factors: hypertension, impaired fasting glucose, low high-density lipoprotein cholesterol, and hypertriglyceridemia. Using a random effects model, we calculated the pooled relative risks (RRs) and 95% confidence intervals (CIs) of incident diabetes.
Results: Our meta-analysis included three studies from the databases plus the NAGALA study, with a total of 134,667 subjects, including 8675 MHO subjects w/o FL and 7218 MHO subjects with fatty liver (wFL). Compared to the metabolically healthy non-overweight subjects w/o FL, the RRs of incident diabetes in the MHO w/o FL and MHO wFL groups were 1.42 (95%CI 1.11–1.77) and 3.28 (95%CI 2.30–4.67).

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Conclusions: Our meta-analysis results demonstrate that the MHO phenotype, with or without fatty liver, presents a risk of the development of type 2 diabetes. Individuals with MHO who do not have fatty liver should be monitored carefully — similarly to those with fatty liver — for the development of diabetes.

Contents

Introduction

Obesity has been known to be a risk factor for type 2 diabetes mellitus since at least the mid-1990s [1,2], and more recent investigations demonstrated that among individuals with obesity, the metabolically healthy obesity (MHO) phenotype presents a low risk of metabolic diseases, such as chronic kidney disease (CKD), compared to the metabolically abnormal obese (MAO) phenotype [3,4]. However, some meta-analyses of the accumulated data regarding the MHO phenotype revealed that having the MHO phenotype presents risks of the development of not only type 2 diabetes [5] but also CKD [6] and cardiovascular disease (CVD) [7,8]. Unfortunately, there are as yet no unified definitions of MHO and MAO [9], which makes the interpretation of meta-analysis results difficult.

A common cause of chronic liver disease, nonalcoholic fatty liver disease (NAFLD) [10], is also a risk factor for type 2 diabetes mellitus [11,12], CKD [13,14] and CVD [15—17]. NAFLD is now considered to be a hepatic manifestation of the metabolic syndrome [18,19]. Many MHO individuals progress to metabolically abnormal obesity over time [20]. On the other hand, the individuals who maintained MHO phenotype was not associated with higher risk of development of diabetes [21,22]. Moreover, a recent study revealed that the existence of fatty liver disease is a risk factor for progression from MHO to the metabolically abnormal phenotype [23], and it is becoming increasingly apparent that the detection of fatty liver disease can play an important role in distinguishing the MHO and MAO phenotypes. Furthermore, we recently revealed the evidence that fatty liver disease has more influence on development of diabetes than metabolic syndrome [24]. Therefore, there is a possibility that the existence of NAFLD is a risk of development of type 2 diabetes in the MHO individuals. Although a pair of investigations indicated that MHO without fatty liver (w/o FL) disease does not present increased risk of diabetes and that MHO with fatty liver (wFL) does increase the risk of diabetes [25,26], a third study showed that

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