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ORIGINAL PAPER

Association of high BMI with subclinical hypothyroidism in young, first-episode and drug-naïve patients with major depressive disorder: a large-scale cross-sectional study

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Abstract

Thyroid dysfunction is known to be associated with obesity, but the reliability of this relationship is easily affected by drug treatment, age, and subclinical hypothyroidism (SCH) with no apparent symptoms. Our research aims to compare obese and overweight BMI ranges with SCH and without SCH in a large sample of young, first-episode and drug-naïve (FEDN) patients with major depressive disorder (MDD), which has received little systemic investigation. A total of 1289 FEDN MDD young outpatients were recruited for this study. Serum thyroid function and lipid level parameters were measured; HAMD and PANSS scales were used to assess patients' depression and positive symptoms. A self-administered questionnaire collected other clinical and demographic data. The prevalence of SCH in FEDN MDD young patients was 58.26%. Compared to patients without SCH, the patients with SCH had a more prolonged illness duration, higher BMI levels, increased prevalence of overweight and obesity, higher HAMD score and PANSS-positive symptom scores, higher levels of TG, TC, LDL-C, and lower levels of HDL-C. Further logistic regression indicated that overweight BMI, obese BMI, illness duration, HAMD score, HDL-C, and TC were significantly associated with SCH. Our results indicate that obesity and overweight may be associated with SCH in young, FEDN MDD patients. The importance of regular thyroid function assessment in young FEDN MDD patients with high BMI should be taken into account.

Keywords Obesity · Overweight · Subclinical hypothyroidism · Major depressive disorder · First-episode drug naïve · Youth

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Introduction

Subclinical hypothyroidism (SCH) is a biochemical state. It is defined by elevated levels of thyroid-stimulating hormone (TSH) in the presence of free thyroxine (FT4) levels within the normal range. The prevalence of SCH has been reported to range from 4 to 20% in adult samples worldwide [1, 2]. Approximately, one-third of people with SCH have no symptoms at all. Symptoms considered to be associated with SCH include overt hypothyroidism: fatigue, muscle cramps, cold sensitivity, and constipation [3]. Other symptoms include poor memory, slowed thinking, puffy eyes, anxiety, and depression [4, 5]. SCH is associated with increased mortality from coronary heart disease, heart failure, and cardiovascular disease [6]. SCH is also a vital factor for the development of overt hypothyroidism [7].

Major depressive disorder (MDD) is a common mental disorder that can lead to poor quality of life [8]. The link between overt thyroid dysfunction and mood abnormalities has been studied. Overt hypothyroidism is one cause of mood disorders, including depression, and may exacerbate dementia [9]. Recent reports have focused on SCH and its potential neuropsychiatric and neurocognitive mechanisms [10]. Patients with SCH are more likely to suffer from depressive symptoms than that of the general population [11]. One study found that some antidepressant treatments reduce patients' serum FT3 and FT4 levels [12]. If patients are at high risk for SCH, there is an extreme risk of developing overt hypothyroidism later in life [13]. Thus, identifying risk factors for subclinical thyroid disease can help clinicians identify individuals at risk and provide immediate treatment to improve patient prognosis.

The coexistence of SCH and MDD suggests that the two disorders have similar clinical features and associations [14]. Several reports have demonstrated an association between SCH and current depressive symptoms, current major depression, and a lifetime history of major depression. A recent meta-analysis showed that SCH was positively associated with the risk of depression [15]. Most available studies report a higher prevalence of SCH or overt hypothyroidism in patients with MDD than in the general population [16]. Fewer studies have reported no association between serum thyroid hormone levels and depressive symptoms [17, 18]. 17.6–30% of patients with SCH will develop overt thyroid disease due to improper treatment. Many signs of overt thyroid disease can aggravate depression and make subsequent treatment more complex, so SCH or mild thyroid dysfunction in MDD patients should receive more attention in clinical practice [19].

Although previous studies have shown that immune dysfunction, environmental factors, and genetic factors are involved in the pathogenesis of SCH, the pathogenesis is not fully understood. Obesity and hypothyroidism are two common clinical conditions in MDD closely linked. Our previous findings suggest that severity of anxiety and depression and higher body mass index (BMI) could be related to elevated TSH levels [20]. This link has become even more relevant in the context of the unprecedented rise in global obesity rates. Obesity is often considered a secondary condition to thyroid dysfunction. New insights suggest that changes in TSH are likely to be a secondary cause of obesity. Recent studies have shown the relationship between obesity and thyroid autoimmunity. The adipocyte hormone leptin appears to be a critical factor. Hypothyroidism is associated with decreased thermogenesis and metabolic rate, increased BMI, and higher obesity rates [21]. There is clinical evidence that even mild thyroid dysfunction in SCH is associated with significant changes in body weight and is a risk factor for overweight and obese BMI ranges; however, this relationship remains murky.

In terms of age, a recent survey found that SCH was related to depression in younger patients but not in older patients [22]. It is widely believed that this mild TSH elevation results from normal aging and is not a true thyroid dysfunction. In addition, mildly elevated serum TSH is commonly seen in the elderly. A handful of studies reported that the relationship between depressive symptoms and SCH is controversial, especially in older patients, as the incidence of SCH increases with age. To avoid the effect of age on this study, we included young patients with first-episode and drug-naïve (FEDN) MDD.

Some previous studies have focused on finding biomarkers associated with abnormal thyroid function in MDD. Researchers are additionally concerned about the relationship between thyroid hormones and obesity. Identifying SCH-associated factors may help clinicians recognize SCH and provide treatment to improve patients' outcomes. However, both thyroid hormone levels and obesity can both be affected by drug therapy. Therefore, this study aimed to identify the relationship between SCH and overweight or obese range BMI in young FEDN MDD patients in a Chinese Han population.

Methods

Subjects

In this cross-sectional study, all patients were recruited from the psychiatric outpatient department of a general hospital in Taiyuan, Shanxi Province, China, from 2015 to 2017. The research was approved for clearance by the hospital's Institutional Review Board (No.Y27). Patients who took part in

this survey all had signed the consent forms. We collected the patient's complete medical history, physical examination, and laboratory tests. Demographic information was collected, including ages, illness duration, age of onset, gender, level of education, marital status, and weight.

The inclusion criteria for MDD patients were the following: (1) age between 18 and 45 years, Han Chinese; (2) confirmed diagnosis of MDD based on the DSM-IV; (3) score of 24 or greater on the HAMD-17; (4) no history of any prior antidepressant or anti-psychiatric treatment; (5) illness duration ≤ 24 months; (6) no history of thyroxine therapy or any specific medications. Patients who met any of the following criteria were excluded: (1) other serious psychiatric diagnoses; (2) alcohol or substance abuse; (3) complications of other physical illnesses; (4) pregnant or breastfeeding; (5) did not agree to sign informed consent.

Clinical interview and assessment

The HAMD-17 was utilized for a comprehensive assessment of depressive symptoms. The scale contains eight items that have five alternative responses: 0, 1, 2, 3, or 4 (none, mild, moderate, severe, very severe), and nine items that have three alternative responses: 0, 1, or 2 (none, mild-moderate, severe). A patient with a setoff score of 24 is considered to have severe depression [23].

The positive subscale of PANSS was used to assess the severity of psychotic symptoms in patients with MDD. Each item was divided into 1 to 7 points (none to extreme seriousness). A total score > 15 was considered to have psychotic symptoms.

In this study, two qualified psychiatrists received training on using these rating scales before the survey. The inter-observer correlation coefficient of over 0.8 was obtained for HAMD and the PANSS-positive subscale scores, respectively, after repeated assessments. They were blind to the clinical status of patients.

Physical and biochemical parameter measurements

The blood samples were collected simultaneously in the morning after an overnight and then immediately sent to the hospital's laboratory center and measured on the same day. This study measured lipids and thyroid function, including HDL-C, LDL-C, TG, TC, FT3, FT4, and TSH. Serum TSH, FT3, and FT4 were measured by chemiluminescent immunoassay. The normal range was 0.27–4.20 mIU/L for TSH, 3.10–6.8 pmol/L for FT3, and 10–23 pmol/L for FT4.

SCH was defined as TSH over 4.2 mIU/L and FT4 levels within the normal range, and according to the definition of SCH, patients were divided into two groups: the group with SCH and the group without SCH. The formula for BMI was used as a weight in kilograms divided by height in meters squared, and patients were classified as normal (BMI < 24), overweight (24 ≤ BMI < 28), or obese (BMI ≥ 28) based on their BMI values [24].

Statistical analysis

We used IBM SPSS 23.0 statistical software to analyze data in the study. Mean standard deviation (SD), median (interquartile range), or percentages (%) were used to describe the data. Analysis of variance (ANOVA), Mann–Whitney test, and Chi-squared test explained the differences in demographic and clinical characteristics between SCH and without SCH. The Bonferroni correction was used to adjust for multiple testing. Further analysis of covariance (ANCOVA) was performed to control for the effects of HAMD, and PANSS-positive scales, HDL-C, TG, TC, and LDL-C on SCH, using BMI as the dependent variable. Significant demographic factors and clinical variables for all participants were included in a multivariate binary logistic analysis to explore the association of SCH in young MDD patients. All p values were calculated at a 2-tailed significance level of <0.05.

Results

Demographic and clinical variables in MDD patients with SCH and without SCH

A total of 1289 subjects were recruited according to the inclusion criteria. The incidence of SCH was 58.26% (751/1289). Table 1 compares the demographic data and clinical variables between patients with SCH and patients without SCH. The results showed significant differences in many variables between the two groups of patients. Compared to patients without SCH, patients with SCH had a longer disease duration ($F = 25.29$, $p < 0.001$), higher HAMD total score ($F = 259.80$, $p < 0.001$), higher positive symptom score ($F = 46.26$, $p < 0.001$), higher BMI level ($F = 38.82$, $p < 0.001$), lower HDL-C level ($F = 91.71$, $p < 0.001$), higher TG levels ($F = 9.59$, $p = 0.002$), higher TC levels ($Z = -16.61$, $p < 0.001$), higher LDL-C levels ($Z = -12.24$, $p < 0.001$), and higher prevalence of overweight and obesity ($X^2 = 45.70$, $p < 0.001$), and these variables all passed the Bonferroni correction (Bonferroni corrected $p < 0.05/14 = 0.0036$). However, there was no significant difference in age, age of onset, level of education, and marriage state between the two groups ($p > 0.05$). Analysis of covariance (ANCOVA) results showed that there was still a statistically significant difference in BMI between the two groups after controlling for other variables such as duration of disease, HAMD total score and PANSS-positive scale score, HDL-C, TG, TC, and LDL-C ($F = 4.95$, $p < 0.001$).

Table 1 Demographic, clinical variables and serum lipid levels between MDD patients with SCH and without SCH

Characteristics	Without SCH ($N=538$)	With SCH ($N=751$)	$X^2/F/Z$	p value
Demographic and clinical characteristics (mean ± SD)				
Age (years)	28.79 (8.58)	29.64 (8.74)	3.05	0.08
Illness duration (months)	4.98 (3.97)	6.13 (4.12)	25.295	<0.001
Age of onset (years)	28.66 (8.52)	29.47 (8.63)	2.85	0.09
HAMD score	28.77 (2.63)	31.19 (2.69)	259.80	<0.001
PANSS-positive symptoms	7.72 (2.76)	9.24 (4.62)	46.26	<0.001
Male, *N* (%)	187 (34.8%)	283 (37.7%)	1.16	0.28
Education, *N* (%)			1.01	0.80
Junior high school	77 (14.3%)	104 (13.8%)		
Senior high school	260 (48.3%)	351 (46.7%)		
College	169 (31.4%)	242 (32.2%)		
Postgraduate	32 (5.9%)	54 (7.2%)		
Unmarried, *N* (%)	208 (38.7%)	279 (37.2%)	0.31	0.58
Biological indicators (mean ± SD)				
HDL-C	1.32 (0.23)	1.17 (0.30)	91.71	<0.001
TG	2.07 (1.03)	2.24 (0.97)	9.59	0.002
TC	4.61 (4.05, 5.12)	5.56 (4.89, 6.29)	−16.61	0.001
LDL-C	2.54 (2.13, 3.10)	3.21 (2.60, 3.70)	−12.24	<0.001
BMI	23.96 (1.75)	24.62 (2.035)	36.82	<0.001
Overweight/obesity, *N* (%)			45.70	<0.001
Normal (BMI < 24)	278 (51.7%)	257 (34.2%)		
Overweight (24 ≤ BMI < 28)	251 (46.7%)	452 (60.2%)		
Obesity (BMI ≥ 28)	9 (1.7%)	42 (5.6%)		

MDD major depressive disorder, *HAMD* Hamilton depression rating scale, *PANSS* Positive and negative syndrome scale, *BMI* body mass index, *TC* total cholesterol (mmol/L), *HDL-C* HDL cholesterol (mmol/L), *TG* triglycerides (mmol/L), *LDL-C* LDL cholesterol (mmol/L)

Associated factors related to SCH by multivariate binary logistic analysis

Table 2 shows the results of multivariate logistic regression analysis. The characteristics independently associated features with SCH in MDD patients were longer disease duration (OR = 1.07, $p < 0.001$), higher HAMD total score (OR = 1.22, $p < 0.001$), lower HDL-C levels (OR = 0.16, $p < 0.001$), higher TC levels (OR = 1.93, $p < 0.001$), more overweight (OR = 2.14, $p < 0.001$), and obesity (OR = 4.12, $p = 0.001$).

Table 2 Associated factors related to SCH by multivariate binary logistic analysis in MDD patients

Variables	*B*	Wald statistic	p value	OR	95% CI
Illness duration (months)	0.07	15.31	<0.001	1.07	1.04–1.11
HAMD score	0.20	36.54	<0.001	1.22	1.14–1.31
PANSS-positive symptoms	0.01	0.06	0.80	1.00	0.96–1.05
TG	−0.07	0.93	0.34	0.93	0.81–1.07
TC	0.66	44.27	<0.001	1.93	1.59–2.33
HDL-C	−1.86	48.04	<0.001	0.16	0.09–0.26
LDL-C	0.15	2.14	0.14	1.17	0.95–1.43
Overweight (24 ≤ BMI < 28)	0.76	29.70	<0.001	2.14	1.63–2.82
Obesity (BMI ≥ 28)	1.42	11.48	0.001	4.12	1.82–9.33

MDD major depressive disorder, *HAMD* Hamilton depression rating scale, *PANSS* Positive and negative syndrome scale; *BMI* body mass index, *TC* total cholesterol (mmol/L), *HDL-C* HDL cholesterol (mmol/L), *TG* triglycerides (mmol/L), *LDL-C* LDL cholesterol (mmol/L)

Discussion

Several studies investigated the relationships between obesity and thyroid function, mainly because of possible etiopathogenetic and therapeutic implications. However, no study has explored the association of obese or overweight BMI range with SCH in young first-episode drug-naïve outpatients with MDD.

Our study showed that the prevalence of SCH in young people with depression was 58.26%, which was much higher than that in the general population. It is consistent with previous studies showing that SCH is associated with an increased risk of depression [25]. A previous meta-analysis showed that SCH was associated with depression in young patients but not in elderly patients [22]. One reason for this could be that a shift in the serum TSH distribution curve toward higher levels during normal aging may misclassify older SCH patients. Estimates of the prevalence of SCH vary by gender, age, race/ethnicity, and geographical location (range: 0.4–16.9%) [26]. In addition, based on the variable definition of SCH, it is difficult to determine the true prevalence of SCH. A study from Korea showed that SCH's prevalence was 9.4% with depression [25], which is much lower than our result. It is worth noting that these results are from different studies that used different TSH reference ranges and had different inter-trial and intra-trial values [27]. Other methods used to obtain the reference ranges for laboratory tests could also explain this phenomenon. Approximately 90% of SCH patients have TSH levels between 4 and 10 mIU/L (μIU/mL) [28], which is of great interest since some researchers have insisted that a value of 10 mIU/mL is a reasonable threshold value, and patients will be evaluated or treated [29].

The duration of depression in young people with SCH was found to be longer in our study, similar to results in studies of adolescent depression [30]. Moreover, depressive symptoms and anxiety symptoms in patients with SCH were more severe than those without SCH, consistent with the results of Lang et al. [20]. However, a prospective study by Kim et al. explored no association between severe SCH during the 2-year follow-up period and the overall risk of depression or any depressive symptoms in middle-aged adults without depression [25]. The participants were primarily middle-aged and generally healthy males and females in Korea, so this may not generalize to other races or age groups. In summary, it is essential to detect thyroid function for depression, especially in young people in different countries.

Our study found that overweight, obesity, HDL-C, and TC levels were factors independently associated with SCH in young MDD patients. In contrast, serum LDL-C and TG levels were not independently associated with SCH in depressed patients. The results of this study differed somewhat from those of the general population. In a study of the Korean general population, SCH patients are more likely to be obese than non-SCH patients, and after adjusting for age, TC and TG concentrations were positively correlated with TSH concentrations [31]. Another epidemiological study concluded that TC levels were higher in participants in the SCH group than in the non-SCH group [32]. On the contrary, a cross-sectional study including 5319 healthy Chinese individuals found no metabolic risk factors associated with the prevalence of SCH in male participants. In contrast, among female participants, BMI was the only independent predictor of SCH [33].

Our study found that severe depressive and psychotic symptoms were closely associated with SCH. However, there were no previous studies on differential expression of TSH levels in patients with psychotic depression. In an earlier study, 19 patients with psychotic depression and 21 patients with non-psychotic depression had no significant difference in TSH levels, which were at normal levels [34]. This result may be related to the accuracy and method of diagnosing psychiatric symptoms in patients with MDD [20]. Studies on depressive symptoms and thyroid function have had different results. A study in Nepal showed a positive association between thyroid dysfunction and depression severity in 70 patients with first-episode MDD [35]. However, another study has shown no association between elevated TSH and the presence of depression in the general population [36]. Reflections on the association between TSH and depressive symptoms are contradictory due to diverse people and the confounding effects of L-thyroxine medications.

Many previous studies are consistent with our findings [37]. Biondi found that TSH levels are at the upper limit of the normal range or slightly increased in obese children, adolescents, and adults [38]. Serum TSH levels are also positively correlated with BMI. In addition, SCH, due to its association with obesity, may increase ALT and the risk for nonalcoholic steatohepatitis. One study also found that the prevalence of SCH among obese patients was 24.3%, significantly higher than in normal-weight controls [31]. There is clinical evidence suggesting that SCH is linked to significant changes in body weight and is an associated element for overweight and obese BMI [21]. BMI was positively associated with serum TSH levels in adolescents [31]. However, different results were found in a survey of 404 children and adolescents aged 5 to 18 years. There was no significant difference in BMI in the SCH patient group than those with normal TSH levels [39]. Song et al. carried out a systematic review and meta-analysis, which found that obesity was significantly related to hypothyroidism, implying that prevention of obesity is crucial for thyroid disorders [40].

These findings could have several explanations. First, one theory suggests that increased deiodinase activity leads to

a high T4 to T3 conversion rate. This has been considered a defense mechanism in obese individuals, able to counteract fat accumulation by increasing energy expenditure [41]. Several studies in animal models have examined the relationship between SCH and MDD [42, 43]. An animal study showed that hippocampal T3 density was slightly lower in rats in the SCH group than in the sham-operation (control) group, suggesting that rats with SCH have dysfunctional thyroid hormone levels despite having plasma thyroid hormones in the normal range. Another possible mechanism is a compensatory increase in TSH and FT3 secretion to overcome the reduced tissue responsiveness to circulating thyroid hormones due to reduced expression of TSH and thyroid hormones in adipocytes of obese individuals [39]. Some studies have shown that TSH sensitivity to thyrotropin-releasing hormone (TRH) is higher in obese patients than in normal-weight patients. Compared to normal-weight patients, obese patients secrete more TSH after taking the TRH [31, 44]. A negative association between FT4 and BMI has been reported, even when FT4 remains within the normal range [45]. In mildly overweight individuals with a physiologically normal thyroid, fat accumulation is associated with lower FT4 and higher TSH levels, resulting in a positive association between TSH and weight gain over time [46]. Altered thyroid function regulated by regular feedback may lead to altered energy expenditure and subsequent BMI changes and weight gain. Just as well, there is biological variation in TSH levels. Stress may induce a variety of neurochemical and hormonal changes, including in the thyroid hormones. Simultaneously, repeated exposure to stressful events is also a potent associated factor for depression. Levels may rise in response to stress and transient disease [47].

Another meaningful consequence of this relationship could be the inflammatory process. Obesity is a chronic, low-grade inflammatory process, and therefore cytokines and other inflammatory markers such as IL-1, IL-6, and TNF-α are increased in overloaded adipose tissue [48]. These increased inflammatory cytokines may cause inhibition of the mRNA expression of the sodium/iodide cotransporter, which—in turn—affects the iodine uptake activity of human thyroid cells [41]. These cytokines may also induce increased thyroid vasodilatation and permeability, thus causing morphological and functional changes in the thyroid gland. Several other studies have found that this chronic inflammatory state of obesity may also affect thyroid function by regulating the expression and activity of deiodinase [49]. The above study may partially explain the mechanisms by which obesity can induce hypothyroidism. In addition, most studies have only explored the association between obesity and thyroid disease, with little investigation into whether thyroid dysfunction is a cause or a consequence of obesity, which requires further prospective cohort and causality studies to investigate.

In addition, the levels of leptin and brown adipose tissue (BAT) are other potential causes. In the case of the former, leptin acts to concentrate the amount of fat currently stored, decreasing appetite and food intake. A high level of leptin in obese patients has also been found to stimulate TRH transcription centrally, thus TSH as a product of the hormonal cascade. Leptin also enhances deiodinase activity, leading to a high rate of T4 to T3 conversion [50]. Concerning the latter, BAT with thermogenic activity has been identified in adults. In recent years, the presence of BAT has been considered an essential target in the treatment of obesity. Energy homeostasis in BAT is primarily influenced by thyroid hormone signaling. Activation of BAT increases energy expenditure through thermogenesis and thus works against obesity. Elevated TSH levels inhibit the "browning" of white fat and reduce energy expenditure, thus promoting excessive fat growth and causing obesity [51].

Limitations of the study should be articulated to better understand from where future studies can pick up. First, the outpatients were recruited from the clinic, all of them being of Han Chinese ethnicity. Therefore, our results should be validated in other populations with different ethnic and clinical backgrounds. Second, the cross-sectional design of our study cannot explain the causal relationship between SCH and overweight or obesity in young patients with depressive disorders, so prospective cohort studies should confirm this relationship. Third, factors such as childhood trauma, various lifestyle choices, family income, and social status may affect the relationship between depression and SCH and were not controlled for in this study. Futures studies incorporating more confounding factors will help to clarify the mechanisms underlying their associations. Fourth, in the current study, the thyroid function of the patients before the onset of depression was unknown; thus, it is difficult to clarify whether SCH precedes the occurrence of depression or occurs as a result of depression. In addition, the diagnosis of SCH is usually based on a single assessment of TSH without a second validated measurement. This approach may lead to potential disqualification of regular thyroid hormone participants as having SCH even though they have only transiently elevated serum TSH levels. Further studies should follow up thyroid function parameters to obtain an accurate diagnosis.

In conclusion, we found a 58.26% prevalence of SCH in young people with MDD. Our results show that overweight and obese BMI are associated with SCH in young depressed patients. Considering the poor health status of patients with MDD and comorbid SCH, thyroid function should be considered in these patients. Routine examination of thyroid function is recommended in young depressive disorder patients, especially in those patients with overweight and obese BMI ranges.

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Author contributions Chuanyi Kang, Yue Zheng, Jiacheng Liu, Xiangyang Zhang, and Na Zhao were responsible for study design, statistical analysis, and manuscript preparation; Xiaohong Wang, Li Ying Yang, Siyu Qiu, and Ying Zhao were responsible for the data curation. Blake N, Lackey, Hanjing Wu, and Xiangyang Zhang were involved in evolving the ideas and editing the manuscript. All the authors have contributed to and have approved the final manuscript.

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Availability of data and materials The data that support the findings of this study are available from the corresponding author X.Y.Z. upon reasonable request.

Code availability Not applicable.

Declarations

Conflict of interest No conflict of interest was disclosed for each author.

Ethical standard The research was approved for clearance by the First Affiliated Hospital of Shanxi Medical University's Institutional Review Board (No. Y27).

Consent to participate Written informed consent was obtained from individual or guardian participants.

Consent for publication Not applicable.

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