Lack of Association Between Depression and Subclinical Hypothyroidism in Adolescents Presenting for Routine Physical Examinations

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ABSTRACT

BACKGROUND: There are conflicting results in the existing studies regarding the association between depression and subclinical hypothyroidism in adolescents. Subclinical hypothyroidism is defined as elevated thyroid stimulating hormone (TSH) levels above the reference range without signs or symptoms of hypothyroidism.

OBJECTIVES: The focus of this study is to determine whether there is any association between depression and subclinical hypothyroidism, (as defined by the serum TSH levels) in a population of healthy adolescents.

DESIGN: Quantitative-based cross-sectional study of a representative subset of the adolescent population.

METHODS: We carried out a cross-sectional study to determine the association between major depressive disorder (MDD) and subclinical hypothyroidism, in adolescents presenting for annual physical examinations during the peak period of the COVID-19 pandemic in the USA, a period deemed high for adolescent depression. All the adolescents were screened for depression by the PHQ-9 screening tool and had their TSH measured.

RESULTS: Of the 304 subjects analyzed, 179 (58.88%) were minimally or not depressed according to the Patient Health Questionnaire (PHQ-9) screening tool (mean PHQ 1.80 ± 1.49). 70 (23.03%) had mild depression (mean PHQ 6.59 ± 1.46), 50 (16.45%) had moderate depression (mean PHQ 13.70 ± 2.75), and 5 (1.64%) had severe depression (mean PHQ 21.40 ± 1.67). Mean TSH values were 1.93 ± 0.99, 1.77 ± 1.05, 2.10 ± 0.98, and 1.57 ± 0.32 mIU/L, respectively in the four groups. All values were within the recommended range of 0.50 to 4.30 mIU/L, without statistically significant inter-group differences.

CONCLUSION: We conclude that there is no statistically significant association between depression and subclinical hypothyroidism, in a population of adolescents presenting for physical examinations, and if the screening for depression by the PHQ-9 tool indicates depression, a screening TSH test for subclinical hypothyroidism is not justified.

KEYWORDS: Adolescents, Covid-19 Pandemic, depression, hypothyroidism, psychology, prevention and control

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Introduction

Adolescent depression is a considerable source of impairments in the US.[1] Children and adolescents with major depressive disorder (MDD) are facing more difficulties interacting with others and have a reduced likelihood of success with their academic achievement.[2] Previous studies also show that the normal development of adolescents can be negatively influenced by depression.[3] Prior to the COVID-19 pandemic, the incidence of adolescent depression was 9% to 12.9%.[1-3] During the COVID-19 pandemic, the global incidence of adolescent depression and anxiety had increased to 25.2% according to a meta-analysis by Racine et al.[4]

According to The American Academy of Pediatrics (AAP) Guidelines for Adolescent Depression in Primary Care (GLAD-PC) statement, all youth 12 years and older presenting for annual health maintenance visits should be screened for depression with a depression-specific tool.[5] In addition, the AAP Bright Futures Program, as well as the Medicaid Early and Periodic Screening Diagnosis and Treatment (EPSDT) program, suggests to regularly screen youth for depression at periodic age-appropriate intervals.[6,7] The US Preventive Service Task Force (USPSTF) and the GLAD-PC guidelines both recommend the Patient Health Questionnaire (PHQ-9) as an effective screening questionnaire to detect adolescent depression.[5,8]

The association between depression and hypothyroidism has been well established by previous studies. However, the association between depression and subclinical hypothyroidism is not well established according to the studies to date. In subclinical hypothyroidism, the TSH level in the serum is typically mildly elevated outside the reference ranges before the serum thyroxine levels become abnormal.[9,10] Furthermore, patients

with subclinical hypothyroidism are usually asymptomatic.[11] According to Helfand and Crapo,[12] the serum TSH had a sensitivity above 98% and a specificity of greater than 92% when used to confirm suspected thyroid disease. Therefore, the serum TSH level is considered the gold standard for assessing thyroid function.[13]

The prevalence of subclinical hypothyroidism differs greatly depending on the patients age, gender and suboptimal iodine measure, with ranges from 3% to 15%.[14] Research has also shown that older populations and female patients were more likely to have a higher prevalence.[15]

Data published in 2021 from the National Health and Nutrition Examination Survey (NHANES) showed that there was no association between subclinical hypothyroidism and depression risk in a sample of US adults which was deemed representative of the overall national population.[9] In their meta-analysis study on the association between hypothyroidism and clinical depression in the general population, Bode et al[16] have reported that the association between hypothyroidism and clinical depression was much less than commonly believed, and the potential connection was more likely higher for female patients and individuals diagnosed with hypothyroidism. In a meta-analysis by Zhao et al,[17] the authors concluded that subclinical hypothyroidism (SCH) is not connected to depression. However, a subgroup analysis according to age found that SCH is related to depression in younger patients, and not so significantly in older patients. However, in a nationwide cross-sectional study in children and adolescents in Germany, Hirtz et al have reported that thyroid dysfunction and thyroid autoimmunity have no effect on mental health and health-related quality of life.[18,19]

There are conflicting results in the studies to date, regarding the association between depression and subclinical hypothyroidism in adolescents. Most often quoted studies to date on this specific subject have been focused on adults (Bode et al[16]) on dataset from Europe (Hirtz et al[18]) and on datasets prior to Covid-19 (Hirtz et al[19], data sets are dated between 2003 and 2017). The objective of this study is to determine whether there is any association between depression and subclinical hypothyroidism (as defined by the serum TSH levels), in a population of healthy adolescents presenting for routine physical examinations during the COVID-19 pandemic in California.

Design

Quantitative-based cross-sectional study of a representative subset of the adolescent population.

Subjects and methods

The study was conducted between September 8th, 2020 and November 3rd, 2021 in a community based, pediatric and adolescent medicine practice in Huntington Beach, CA, USA. The study participants are consecutive adolescents 13 to 19 years of age, presenting for routine physical examinations during the study period. Adolescents with acute or chronic medical problems, abnormal physical examinations, abnormal labs, those taking any medications, and those with a history of thyroid disease and depression were excluded. At time of presentation, detailed history, complete physical examination, and standard labs including complete blood count (CBC), Comprehensive Metabolic Panel (CMP), fasting blood sugar (FBS), 25 hydroxy vitamin D level, and urinalysis were done.

All the adolescents were screened for depression by the PHQ-9 screening tool. According to guidelines, those with a PHQ score of 4 or less were classified as minimally or non-depressed. Those with a score of 5 to 9 as mild, 10 to 19 as moderate, and 20 to 27 as severe.[20-22]

All adolescents had their TSH measured. Those with TSH greater than 4.30 were classified as being elevated and being sub clinically hypothyroid. (Normal range 0.50–4.30 mIU/L Quest labs, Immunoassay) per the standard reference range established by the QUEST labs.

Prior to recruitment for this study, all the adolescents and their parents provided written informed consent. The pediatric peer review committee at Fountain Valley Regional Hospital in California deemed it not necessary to request a formal ethics approval for carrying out this study.

Statistical analysis

All statistical analyses were performed using the R software environment for statistical computing and graphics (version 4.2.1). Associations between categorical variables were assessed using Fisher's exact test for count data, computed using the Fisher.test () function. Distributions of continuous variables in two or more samples were compared using either the Kruskal-Wallis rank sum test (>2 groups), computed using the Kruskal.test () function, or the Mann-Whitney test (two groups), computed using the Wilcox.test () function. Spearman's rank correlations were computed using the Cor.test () function, with the method parameter set to "spearman." Reported *P*-values are not adjusted for multiple comparisons and $P < .05$ is used as a significance threshold.

Results

During the study period, 332 consecutive adolescents presented for routine physical examinations (PE). The flow chart for patients excluded and those eligible for analysis is in Figure 1.

Baseline demographics of the four groups are as in Table 1.

304 adolescents were eligible for the study analysis. 179 (58.88%) of the eligible subjects had minimal or no depression (mean PHQ score 1.80 SD ± 1.49). Of the 125 depressed adolescents (41.12% of study population), 70 (23.03% of study population) were mild (mean PHQ score 6.59 SD ± 1.46) 50 subjects (16.45% of study population) were moderate (mean PHQ score 13.70 SD ± 2.75), and 5 subjects (1.64% of study population) had severe depression (mean PHQ 21.40 SD ± 1.67). The mean TSH ± SD in the four groups are as in Table 2.

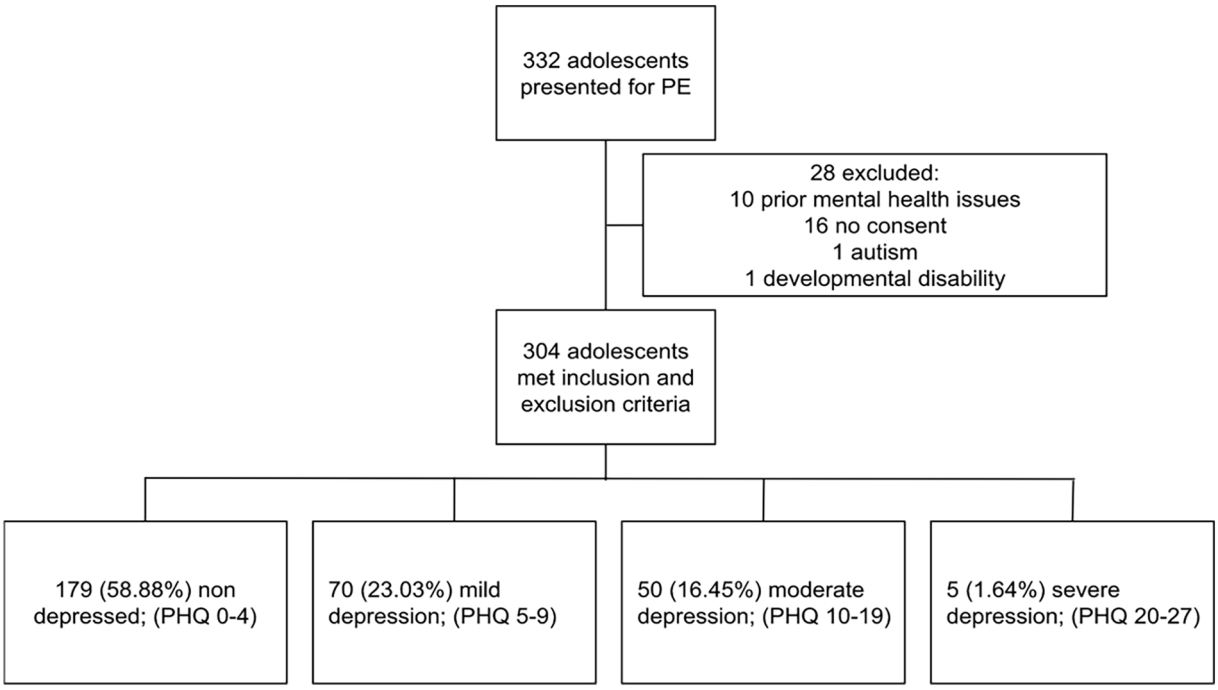

Figure 1. Flow Chart of Patient Sample.

Table 1. Baseline characteristics of study groups (n = 304).

PARAMETER	NON-DEPRESSED	MILD	MODERATE	SEVERE
	N = 179	N = 70	N = 50	N = 5
Ethnicity H/C/A/AA	H: 157 (87.71%)	H: 64 (91.43%)	H: 41 (82%)	H: 2 (40%)
	C: 11 (6.15%)	C: 3 (4.29%)	C: 6 (12%)	C: 3 (60%)
	A: 10 (5.59%)	A: 3 (4.29%)	A: 3 (6%)	A: 0 (0%)
	AA: 1 (0.56%)	AA:0 (0%)	AA: 0 (0%)	AA: 0 (0%)
Female (%)	41.90%	57.14%	74.00%	80.00%
Male (%)	58.10%	42.86%	26.00%	20.00%
Mean age ± SD	15.71 ± 1.83	15.36 ± 2.19	15.62 ± 1.79	15.20 ± 1.30
Mean BMI ± SD	71.80% ± 29.63	75.20% ± 29.31	77.14% ± 25.50	77.40% ± 30.15

Abbreviations: A, Asian; AA, African American; C, Caucasian; H, Hispanic.

Ethnicity shows some association with depression status (Fisher's exact test $P = .04349$), though this appears to be driven by the shifted ethnicity distribution in the limited subset of 5 patients with severe depression; excluding the latter, there is no association ($P = 0.6836$). Gender and depression status are associated (Fisher's exact test $P = .0001362$), with the distribution of PHQ-9 test scores shifted toward higher values in female patients (25th, 50th, 75th percentiles, females vs. males: [2, 5, 10] vs. [1, 3, 5]; Mann-Whitney test $P = .0002909$). The distributions of ages and BMI do not differ significantly across depression status groups (Kruskal-Wallis rank sum test $P >> .05$).

The distribution of TSH levels does not differ significantly between depression status groups (Kruskal-Wallis rank sum test $P = .07757$), with all distributions lying substantially within the normal range (0.50–4.30 mIU/L). There is no trend toward higher PHQ-9 test scores in patients with higher TSH levels (PHQ-9 score vs. TSH, Spearman's rank correlation rho = −0.03777; $P = 0.5118$) (Figure 2).

Discussion

According to the recommendations from the AAP, Primary Care Providers (PCP) routinely screen for depression in adolescents when they present for annual physical examinations.

Table 2. PHQ scores and TSH values in the 4 groups.

	NON-DEPRESSED	MILD	MODERATE	SEVERE
Mean PHQ (±SD)	1.80 ± 1.49	6.59 ± 1.46	13.70 ± 2.75	21.40 ± 1.67
Mean TSH (±SD)	1.93 ± 0.99	1.77 ± 1.05	2.10 ± 0.98	1.57 ± 0.32

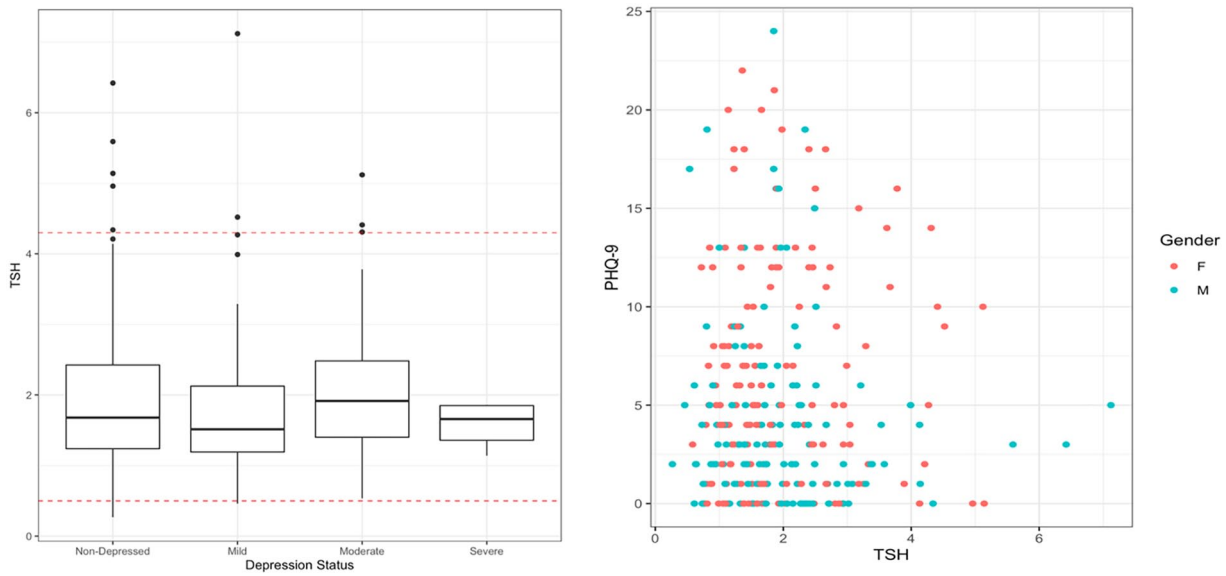

Figure 2. Association of TSH levels with depression status measures.
Distribution of TSH levels in depression status groups (left graph). Red dashed lines indicate the normal range (0.50–4.30 mIU/L). Boxed regions span the interquartile range (IQR) between the 25th and 75th percentiles, with the median TSH value indicated by a bold line. Lines from the boxes extend to either 1.5 times the IQR, or up to the farthest observation within this range. Outlying observations beyond the IQR-based ranges are plotted directly. PHQ-9 test scores versus TSH level (right graph).

If screening tests such as the PHQ-9, indicate depression, it is customary to work up for comorbidities such as hypothyroidism. In our study of the 304 adolescents who met the inclusion and exclusion criteria, 58.88% were minimally or not depressed, while 41.12% were depressed according to the PHQ-9 scoring system. The majority of the depressed adolescents were in the mild group (70 of 125 subjects 56%) while 50 of 125 (40%) subjects were moderate and 5 of 125 (4%) were severely depressed. The 41.12% prevalence of adolescent depression in our population appears to be much higher than the 25.12% prevalence of adolescent depression observed globally during the COVID-19 pandemic, as reported in the Journal of the American Medical Association Pediatrics of November 2021.[4] This could be due to our sample being more ethnically homogeneous (over 80% Hispanics) and containing more vulnerable socioeconomic groups relative to the larger and more diverse population evaluated in the JAMA study. All the participants were on Medicaid (i.e., MediCal for California) which implies that they had a lower socio-economic status (SES). There are several studies indicating that the COVID-19 pandemic had a significant impact on mental health and certain populations including Hispanic and lower SES adolescents were particularly vulnerable to increased depression rates.[23,24]

In our study, serum TSH levels, used to assess subclinical hypothyroidism, were within the normal range and did not differ significantly in the non/minimal, mild, moderate, or severely depressed groups.

Conclusion

This study contributes to the scarce body of literature, and the takeaway from this study indicates that based on cross sectional data analysis there is no statistically significant association between depression and subclinical hypothyroidism, in a population of adolescents from Southern California presenting for routine physical examinations during the COVID-19 pandemic.

In practice, our data indicates that in healthy adolescents presenting for routine physical examinations, and if the screening for depression by the PHQ-9 tool indicates depression, a screening TSH test for subclinical hypothyroidism is not justified.

Our study was limited by the small sample size and the population being primarily of Hispanic ethnicity with also lower SES, hence the results might not be applicable to the general US adolescent population. Large scale cross-sectional studies are warranted to definitely ascertain whether adolescent depression is associated with subclinical hypothyroidism.

Declarations

Ethics approval and consent to participate

All the adolescents and their parents provided written informed consent. The pediatric peer review committee at Fountain Valley Regional Hospital in California deemed that it was not necessary to request a formal ethics approval for carrying out this study.

Consent for publication

Patients signed consents.

Author contributions

Mohan Kumaratne: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing.

Franck Vigneron: Conceptualization; Methodology; Project administration; Resources; Visualization; Writing—original draft; Writing—review & editing.

Jasmine Cisneros: Data curation; Investigation; Resources; Software; Validation; Writing—original draft.

Vinodh Rajapakse: Data curation; Formal analysis; Investigation; Methodology; Software; Validation; Writing—original draft; Writing—review & editing.

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Availability of data and materials

All data generated or analyzed during this study are included in this article.

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