Association of Thyroid Function with Suicidal Behavior: A Systematic Review and Meta-Analysis

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Abstract: Thyroid disease is a very common condition that influences the entire human body, including cognitive function and mental health. As a result, thyroid disease has been associated with multiple neuropsychiatric conditions. However, the relationship between thyroid dysfunction and suicide is still controversial. We conducted a systematic review and meta-analysis to describe the association of thyroid function with suicidal behavior in adults. We searched four data bases (MEDLINE, EMBASE, PsycINFO, and Scopus) from their inception to 20 July 2018. Studies that reported mean values and standard deviation (SD) of thyroid hormone levels [Thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), total thyroxine (TT4), and total triiodothyronine (TT3)] in patients with suicidal behavior compared with controls were included in this meta-analysis. The abstracts and papers retrieved with our search strategies were reviewed independently and in duplicate by four reviewers for assessment of inclusion criteria and data extraction, as well as for evaluation of risk of bias. Random-effects models were used in this meta-analysis to establish the mean difference on thyroid function tests between groups. Overall, 2278 articles were identified, and 13 studies met the inclusion criteria. These studies involved 2807 participants, including 826 participants identified with suicidal behavior. We found that patients with suicide behavior had lower levels of FT3 (−0.20 pg/mL; p = 0.20) and TT4 (−0.23 µg/dL; p = 0.045) compared to controls. We found no differences in either TSH, FT4, or TT3 levels among groups. With our search strategy, we did not identify studies with a comparison of overt/subclinical thyroid disease prevalence between patients with and without suicide behavior. The studies included in this meta-analysis had a low-to-moderate risk of bias. In the available literature, the evidence regarding the association of thyroid disorders and suicidal behavior is limited. We found that patients with suicidal behavior have significantly lower mean FT3 and TT4 levels when compared to patients without suicidal behavior. The clinical implications and pathophysiologic mechanisms of these differences remain unknown and further research is needed.

Keywords: suicide; thyroid function; hypothyroidism; hyperthyroidism
1. Introduction

Suicide is one of the main causes of mortality around the globe, accounting for about 800,000 deaths every year [1]. Deaths by suicide are more frequent in individuals with psychiatric disorders, such as major depression and alcohol use disorder. By far the single most important risk factor for suicide is a prior suicide attempt [2]. Therefore, suicide and suicide attempt/ideation are serious public health problems, as these disorders deeply affect families and communities and have long-lasting effects on the people left behind.

Thyroid dysfunction is the most common endocrine disorder [3]. Most current estimates showed that around 12% of Americans will develop a thyroid condition during their lifetime and that around 20 million have a thyroid disorder [4]. Additionally, it has been estimated that one in eight women will develop a thyroid disorder during their lifetime [5]. Some endocrine disorders have been correlated with psychiatric conditions, such as major depression, anxiety, etc. [6–9]. This is not the case for suicidal behavior, as its relationship with thyroid dysfunction is controversial, and mostly based on observational studies.

A nationwide Danish register-based study, including 111,565 participants, reported that mortality due to suicide was increased (0.10% vs. 0.07%, \( p < 0.001 \)) in patients with Hashimoto’s thyroiditis compared to matched controls, suggesting a possible role of Hashimoto’s thyroiditis in the pathophysiologic mechanisms of suicidal behavior [10]. Similarly, a study including 1718 patients with a history of major depressive disorder showed that those with history of suicide attempt had higher levels of thyroid-stimulating hormones (TSH) and thyroid autoantibodies compared with those without history of suicide attempt, suggesting a potential role of alterations in thyroid function tests in the risk of suicide attempts [11]. In contrast, in a large prospective cohort study of women with thyroid dysfunction that explored the risk of cause-specific mortality after nearly 30 years of follow-up, neither hyperthyroidism nor hypothyroidism were associated with higher rates of suicide [12].

Due to the scarcity of evidence and the conflicting findings among observational studies, we conducted, to our knowledge, the first systematic review and meta-analysis exploring the association between thyroid dysfunction with suicidal behavior in adults.

2. Materials and Methods

2.1. Search Strategy

We conducted a comprehensive search in four data bases (Ovid MEDLINE Epub Ahead of Print, Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid, PsycINFO, and Scopus) from their inception to 20 July 2018, with no language restrictions. Our search strategy was designed and conducted by an experienced librarian (P.E.J.) with input from the principal investigator (S.M.) (File S1).

A systematic review software (DistillerSR, Ottawa, ON, Canada) was used to upload the results of the search strategies, for title and abstracts screening, and for full-text review. Each paper was reviewed by two reviewers working in an independent manner. First, we screened abstracts for eligibility, and those that could be potentially included in our meta-analysis underwent an in-depth review of the full-text paper. The chance-adjusted interreviewer agreement among reviewers was high (kappa statistic = 0.82). Any disagreement during the reviewing process was resolved by the principal investigator (S.M.).

2.2. Study Selection

For this systematic review and meta-analysis, studies reporting mean values of thyroid function tests [TSH, free thyroxine (FT4), free triiodothyronine (FT3), total thyroxine (TT4), and total triiodothyronine (TT3)] along with their standard deviation (SD) in patients with suicidal behavior (recent episode or history of suicidal ideation/suicide attempt) compared with patients without suicidal behavior were included. We contacted the authors of those papers in which additional information or clarification was required in order to confirm eligibility. In cases where we were not able to reach them, these studies were excluded from the analyses. Studies with only abstracts available, papers published in languages other...
than English or Spanish, papers without a quantitative assessment of thyroid function, and papers without a comparison to a control group (group without suicidal behavior) were excluded.

2.3. Data Extraction and Quality Assessment

We designed and used a standardized form to retrieve data from each study included in the meta-analysis. The data extracted included: first author name, paper title, publication year, country, publishing journal, study design, type and criteria used to define the group with suicidal behavior and control group, sample size of suicidal behavior group and control group, mean and SD of age by groups, percentage of female by groups, and mean and SD of thyroid function tests (TSH, FT4, TT4, FT3, TT3) by groups. The data from each paper were extracted independently and in duplicate by four reviewers.

For the assessment of methodological quality and risk of bias of the included studies we used the Newcastle-Ottawa risk of bias tool for observational studies [13]. This tool has been extensively validated and is used to assess the comparability of the study groups, their representativeness, and the ascertainment of exposure and outcomes. Reviewers worked independently, assessing the risk of bias of the included studies. Any disagreement during this stage was resolved by consensus.

2.4. Statistical Analysis

The main outcomes summarized in this meta-analysis were the mean difference (MD) in thyroid function tests for the suicidal behavior group compared with the control group. We calculated and pooled unstandardized MDs of the included studies using random effects models [14]. In the case of multiple subgroups from one study sharing the same comparison group, these groups were combined following the recommended procedure [14]. We used the $I^2$ statistic to estimate the percentage of total between-study variation due to heterogeneity rather than chance [14]. Sensitivity analyses, when possible, were performed according to the type of suicidal behavior of the study population (recent suicide attempt, recent suicidal ideation, history of suicidal attempt, history of suicidal ideation). We performed leave-one-out sensitivity analyses by iteratively removing one study at a time and recalculating the summary MD for those outcomes assessed in $\geq 10$ studies. We assessed publication bias with funnel plot for visual detection of asymmetries and Egger’s tests for the detection of statistical asymmetry in the funnel plot when $\geq 10$ studies were available for a specific outcome [15,16]. All values are two-tailed, and $p < 0.05$ was set as the threshold for statistical significance. Review Manager v5.4, OpenMeta[Analyst], and IBM SPSS statistics v26 were used for statistical analyses.

3. Results

3.1. Study Selection and Characteristics

Our search strategies identified 2278 articles, of which 102 were evaluated as full text and 13 studies [17–29] were finally selected for the meta-analysis (Figure 1). Table 1 summarizes the characteristics of the studies included in the meta-analysis. These studies involved 2807 participants, of whom 826 participants had suicidal behavior. Sample sizes ranged from 20 to 555 participants; mean ages of the participants ranged from 23 to 50 years. All the included studies reported thyroid function tests as mean and SD for the suicidal behavior group compared with control group. The studies included in this meta-analysis have a low-to-moderate risk of bias (Supplementary Table S1).
3.2. Suicidal Behavior and Thyroid Function Tests

We found that patients with suicidal behavior had significantly lower levels of FT3 (−0.20 pg/mL; 95% CI, −0.37 to −0.03; p = 0.02; I² = 89%) and TT4 (−0.23 µg/dL; 95% CI, −0.46 to −0.005 µg/dL; p = 0.045; I² = 0%) compared to controls (Figure 2). There were no differences in the levels of TSH (−0.07 mIU/L; 95% CI, −0.25 to 0.12; p = 0.46; I² = 73%), FT4 (−0.04 ng/dL; 95% CI, −0.17 to 0.09; p = 0.56; I² = 96%) and TT3 (0.71 ng/dL; 95% CI, −4.61 to 6.02; p = 0.79; I² = 0%) (Figure 2). We did not identify studies with a comparison of overt/subclinical thyroid disease prevalence in patients with and without suicide behavior.

Figure 1. PRISMA flow diagram.
Table 1. Characteristics of the included study groups.

| First Author | Publication Year | Country | Study Type | N     | Female (%) | Mean Age (SD) | Suicidal Behavior Group | Group Description | Control Group | Mean Age (SD) | Group Description |
|--------------|------------------|---------|------------|-------|------------|---------------|-------------------------|-------------------|---------------|---------------|-------------------|
| Baek         | 2014             | South Korea | Cross-sectional | 91    | 78.0       | 40.1 (NR)     | Patients newly diagnosed with major depressive disorder (Diagnostic and Statistical Manual of Mental Disorders (DSM-IV criteria); recent and lifetime suicide attempts) | The Korean version of the MNI Nonsuicidal Psychiatric Interview (MINI) suicidality module. Three groups: recent suicide attempters (within the last month), lifetime attempters (those who have attempted suicide in their lifetime except for the past month) and never attempters | 464 | 72          | 47.5 (13.6) |
| Berlin       | 1999             | France   | Cross-sectional | 39    | NR         | NR            | Patients with major depressive disorder (DSM-III-R criteria) and necessitating hospitalization-Previous suicide attempt | NR | NR           | NR                |
| Butkusut-Silostoviene | 2018     | Lithuania | Cross-sectional | 56    | 66.1       | 36.5 (13.1)   | Adult non-psychotic patients, without organic brain disorder, hospitalized due to high suicide risk (Suicide ideation or attempt) | An authors' composed socio-demographic questionnaire including questions about history and type of suicidal ideations or behavior. The majority of patients presented after a suicidal attempt (83.9%) and a small percentage with severe suicidal ideations and high risk of suicide (16.1%) | 120 | 42.5        | 34.5 (13.0) |
| Durval       | 2010             | France   | Case/Control  | 53    | 58.5       | 38.3 (10.7)   | Inpatients with current major depressive episode (DSM-IV criteria) and recent suicidal attempt or history of suicidal attempt | Semi-structured interview with an experienced psychiatrist and a review of medical records. Recent suicide attempters if the suicidal act occurred during the current depressive episode. Past suicide attempters, if the most recent suicide attempt had not occurred during the current depressive episode | 42 | 45.2        | 40.9 (13.1) |
| Durval       | 2017             | France   | Case/Control  | 122   | 68         | 39.4 (11.8)   | Adults with major depressive episode (DSM-IV criteria) and with bipolar I disorder, and 9 with bipolar II disorder with a suicidal attempt that occurred within the last ten years | Semi-structured interview with an experienced psychiatrist. Current/recent suicide attempt (occurred within the last year) and in early remission/history of suicide attempts (the last suicide attempt occurred 12-24 months prior to evaluation) | 50 | 62          | 40.2 (9.3)   |
| Jokinen      | 2008             | Sweden   | Case/Control  | 12    | 0          | 32 (7.2)      | Patients not receiving any antidepressant treatment admitted to the hospital after a suicide attempt | The Suicide Intent Scale performed by a psychiatrist within 48 h after admission. The instrument was designed to measure the factual aspects of a suicide attempt | 8  | 0           | 24 (1.8)     |
| Jose         | 2015             | India    | Case/Control  | 7     | 0          | 23.3 (18)     | Male patients with schizophrenia (DSM IV TR criteria) and bipolar I disorder, and who were not on any treatment for schizophrenia for at least four weeks-Suicidal ideation present in the last three months | The Columbia Suicide Severity Rating Scale assessing suicidal ideations and behaviors for recent past (three months) was used | 31 | 0           | 30.3 (7.1)   |
| Khoshid      | 2018             | Pakistan | Cross-sectional | 54    | 39         | 30.5 (10.3)   | Consecutive patients with past history of suicide attempt/ideation | The Korean version of the MINI suicidality module assessing suicidal behavior within the last month | 50 | 44          | NR            |
| Kim          | 2013             | South Korea | Cross-sectional | 112   | 100        | 41.7 (13.9)   | Female patients with major depressive disorder (DSM-IV/TR criteria) and a recent suicide attempt (Suicide ideation or attempt) | The Korean version of the MINI suicidality module assessing suicidal behavior within the last month | 339 | 100         | 49.1 (14.7) |
| Maas         | 1989             | Belgium  | Cross-sectional | 17    | 100        | 48.5 (10.5)   | Female patients with major depressive disorder and suicidal ideation | Suicide ideation was determined when the Hamilton Rating Scale for Depression score on item 5 (suicide) was three, and when the item on suicide of the Structured Clinical Interview for DSM-III (depression section) was definitely positive | 17 | 100         | 50.4 (10.1) |
| Ocean        | 2016             | Turkey   | Case/Control  | 115   | 67.8       | 25.9 (11.6)   | Suicide attempters who were admitted consecutively to the Emergency Room | Evaluation of DSM-IV-TR criteria and details of previous and current psychiatric history within the last six months were recorded by means of a semi-structured interview by a senior and experienced psychiatrist resident | 243 | 68.4a       | 26.4 (6.6a)  |
| Peng         | 2018             | China    | Case/Control  | 49    | 59.9       | 36.4 (15.5)   | Suicidal attempters consecutively admitted after a suicide attempt at a university hospital | The Hamilton Depression Rating Scale and the Beck Scale for Suicidal Ideation | 202 | 61.4        | 36.4 (15.7) |
| Pompili      | 2012             | Italy    | Cross-sectional | 79    | 63.3       | 40.8 (13.9)   | Patients suffering from mood disorders and psychosis consecutively admitted to the emergency department-Suicide attempt | An interview a psychiatrist performing mental examinations relied on the MINI and one section of this instrument dedicated to the assessment of suicidal risk, with questions about past and current suicidality | 360 | 50.6        | 41.8 (13.3) |
### A) TSH

| Study or Subgroup | Suicidal behavior - TSH | Control - TSH | Mean Difference |
|-------------------|-------------------------|---------------|----------------|
|                   | Mean [mIU/L]  | SD [mIU/L]  | Total | Mean [mIU/L]  | SD [mIU/L]  | Total | Weight  | IV, Random, 95% CI [mIU/L] | Mean Difference |
| Berlin, 1999      | 1.5          | 0.9          | 39    | 1.5          | 1.2          | 58    |         |                          | 0.00 [-0.42, 0.42] |
| Bulbule-Siloezone, 2018 | 1.53        | 0.81        | 52    | 1.45         | 0.68         | 110   |         |                          | 0.08 [-0.17, 0.23] |
| Duval, 2010       | 1.1          | 0.57         | 53    | 0.91         | 0.42         | 42    |         |                          | 0.19 [-0.03, 0.41] |
| Duval, 2017       | 1.31         | 0.72         | 122   | 1.15         | 0.62         | 50    |         |                          | 0.16 [-0.05, 0.37] |
| Jokinen, 2008     | 1.6          | 1            | 12    | 1.9          | 0.8          | 8     |         |                          | -0.30 [-1.09, 0.49] |
| Jose, 2015        | 1.52         | 0.03         | 7     | 1.89         | 1.76         | 31    |         |                          | -0.37 [-1.15, 0.41] |
| Khurshid, 2018    | 2.1          | 1            | 52    | 2.3          | 1.1          | 50    |         |                          | -0.20 [-0.91, 0.21] |
| Kim, 2013         | 1.68         | 1.01         | 112   | 1.83         | 1.55         | 339   |         |                          | -0.25 [-0.90, -0.00] |
| Maes, 1989        | 1.25         | 0.8          | 17    | 1.2          | 0.91         | 17    |         |                          | 0.05 [-0.53, 0.63] |
| Oczon, 2016       | 1.96         | 1.26         | 112   | 1.62         | 0.86         | 246   |         |                          | 0.34 [0.08, 0.60] |
| Peng, 2018        | 1.35         | 0.6          | 69    | 1.92         | 1.49         | 202   |         |                          | -0.57 [-0.82, -0.32] |
| Pompili, 2012     | 1.68         | 1.19         | 79    | 2.05         | 3.64         | 360   |         |                          | -0.37 [-0.85, 0.11] |

Total (95% CI) 726 1512 100.0%  -0.07 [-0.25, 0.12]

Heterogeneity: Tau^2 = 0.07; Chi^2 = 40.42, df = 11 (P < 0.0001); I^2 = 73%
Test for overall effect: Z = 0.73 (P = 0.46)

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### B) FT4

| Study or Subgroup | Suicidal behavior - FT4 | Control - FT4 | Mean Difference |
|-------------------|-------------------------|---------------|----------------|
|                   | Mean [ng/dL]  | SD [ng/dL]  | Total | Mean [ng/dL]  | SD [ng/dL]  | Total | Weight  | IV, Random, 95% CI [ng/dL] | Mean Difference |
| Berlin, 1999      | 1.02         | 0.2         | 39    | 1.07         | 0.23         | 55    |         |                          | -0.05 [-0.14, 0.04] |
| Bulbule-Siloezone, 2018 | 1.06       | 0.21        | 52    | 1.3          | 0.17         | 110   |         |                          | -0.24 [-0.31, -0.17] |
| Duval, 2010       | 0.99         | 0.22         | 53    | 1.16         | 0.22         | 42    |         |                          | -0.17 [-0.26, -0.08] |
| Duval, 2017       | 0.94         | 0.24         | 122   | 0.92         | 0.21         | 50    |         |                          | -0.09 [-0.15, -0.01] |
| Jose, 2015        | 1.69         | 0.27         | 7     | 1.41         | 0.2          | 31    |         |                          | 0.25 [0.07, 0.43] |
| Khurshid, 2018    | 1.17         | 0.25         | 52    | 1.17         | 0.17         | 50    |         |                          | 0.00 [0.00, 0.00] |
| Maes, 1989        | 1.20         | 0.22         | 17    | 1.44         | 0.49         | 17    |         |                          | -0.15 [-0.41, 0.11] |
| Oczon, 2016       | 1.37         | 0.34         | 116   | 1.03         | 0.23         | 248   |         |                          | 0.37 [0.30, 0.44] |
| Peng, 2018        | 0.97         | 0.29         | 69    | 1.2          | 0.23         | 202   |         |                          | -0.23 [-0.31, -0.15] |
| Pompili, 2012     | 0.82         | 0.2         | 79    | 0.9          | 0.23         | 360   |         |                          | -0.08 [-0.13, -0.03] |

Total (95% CI) 606 1165 100.0%  -0.04 [-0.17, 0.09]

Heterogeneity: Tau^2 = 0.04; Chi^2 = 220.42, df = 9 (P < 0.000001); I^2 = 96%
Test for overall effect: Z = 0.50 (P = 0.56)

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Figure 2. Cont.
Figure 2. Forest plots summarizing the mean difference of TSH, FT4, TT4, FT3, and TT3 levels in patients with suicidal behavior compared with control group.
In sensitivity analyses according to the type of reported suicidal behavior, we found that, similarly to the overall analysis, significantly lower levels of FT3 were maintained in patients with history of suicide attempt, who also had significantly lower levels of FT4 and higher levels of TSH (Table 2). Contrastingly, significantly lower levels of TSH were found in the group of patients with recent suicide ideation (Table 2).

Table 2. Sensitivity analysis by type of suicidal behavior.

| Sensitivity Analyses                     | MD [95% CI]          | I² (%) | References Included |
|-----------------------------------------|----------------------|--------|---------------------|
| Recent suicide attempt                  |                      |        |                     |
| TSH (mIU/L)                             | −0.03 [−0.28 to 0.22] | 72     | [19–21,23,25,27–29] |
| FT4 (ng/dL)                             | −0.08 [−0.26 to 0.11] | 98     | [19–21,27–29]       |
| TT4 (µg/dL)                             | −0.35 [−0.11 to 0.82] | 0      | [17,25]             |
| FT3 (pg/mL)                             | −0.19 [−0.39 to 0.01] | 91     | [19–21,27–29]       |
| TT3 (ng/dL)                             | −1.41 [−2.73 to 5.54] | 0      | [17,25]             |
| Recent suicidal ideation                |                      |        |                     |
| TSH (mIU/L)                             | −0.30 [−0.51 to −0.09] | 0      | [22,25,26]          |
| FT4 (ng/dL)                             | −0.07 [−0.35 to 0.49] | 84     | [22,26]             |
| History of suicide attempt              |                      |        |                     |
| TSH (mIU/L)                             | 0.18 [0.01 to 0.35]   | 0      | [18,20,21,24]       |
| FT4 (ng/dL)                             | −0.06 [−0.10 to −0.01] | 0     | [18,20,21,24]       |
| FT3 (pg/mL)                             | −0.27 [−0.41 to −0.12] | 22    | [20,21,24]          |

MD, mean difference; CI, 95% confidence interval; TSH, thyroid stimulating hormone; FT4, free T4; FT3, free T3; TT4, total T4; TT3, total T3.

3.3. Publication Bias and Leave-One-Out Sensitivity Analysis

We did not find major asymmetries in the funnel plots to suggest high risk of publication bias (Supplementary Figure S1). For outcomes assessed in ≥10 studies we performed Egger’s tests, TSH (p = 0.43) and FT4 (p = 0.69), which suggested no significant publication bias existed for these outcomes. We performed a leave-one-out sensitivity for those outcomes assessed in ≥10 studies (TSH and FT4 levels) and the summary MDs remained stable (Supplementary Figure S2). This finding indicates that our results were not driven by any single study and that similar results could be obtained after excluding individual studies.

4. Discussion

In this systematic review and meta-analysis, we found that patients with suicidal behavior have lower levels of FT3 and TT4 compared with controls, but we found no difference in TSH, FT4, or TT3 levels. Furthermore, the subgroup of patients with history of suicide attempt had lower FT3 and TT3 levels, and higher TSH levels compared to controls. This study represents the first summary about the relationship between suicidal behavior with thyroid function.

Our results are in line with previously published evidence regarding the risk/association of thyroid disorders with suicide behavior [10,30,31]. Heiberg-Brix et al. found that patients with Hashimoto’s thyroiditis had an increased frequency of death by suicide (HR = 1.31; 95% CI, 1.04–1.65, p = 0.024) compared to euthyroid controls in a register-based Danish study [10]. In contrast, this frequency is not increased in patients with Graves’ disease compared to controls without Graves’ disease or euthyroid controls from the general population [32,33]. According to these findings, suicide possibly has a stronger association with autoimmune hypothyroidism rather than autoimmune hyperthyroidism. Similar results have been reported for suicidal attempt/ideation and thyroid disorders. A cross-sectional study showed that the prevalence of hypothyroidism in a group of 31 patients with bipolar disorder and suicide attempt was higher (25.8%) compared with a prevalence of 15.9% in a group of 63 patients with bipolar disorder with no suicide attempt [30]. Sanna et al. reported a 6.5% prevalence of thyroid disorders in males with history of suicidal ideation, compared with a 1.9% prevalence in males without history of
suicidal ideation [31]. Nevertheless, these results should be analyzed carefully as all these studies are observational with relatively small sample size and analyses are not adjusted for confounders.

The development of suicide, depression, and other affective disorders has been previously associated with autoimmune diseases, including thyroid-specific diseases [10,34–36]. In a meta-analysis published by Siegmann et al., patients with Hashimoto thyroiditis and either subclinical or overt hypothyroidism showed significantly higher scores on standardized depression instruments compared to euthyroid controls [37]. A second meta-analysis published in 2019, found that patients with subclinical hypothyroidism had higher risk of depression than euthyroid controls. However, there was no difference in the mean TSH level between individuals with depression and healthy controls [38]. Although the majority of patients with depression and other mood disorders have completely normal thyroid function tests, several test abnormalities have been described including elevated TT4 levels, low TT3 and FT3 levels, blunted TSH response to thyrotropin-releasing hormone, and positive antithyroid antibodies [36,39–45]. Interestingly, thyroid hormone in the form of liothyronine has been used for the treatment of depression, mainly as an augmentation therapy in severe forms of depression [46–49]. In addition, in the setting of suicidal behavior, there is evidence suggesting that thyroid hormones might have a role in the regulation of the neurotransmitters involved in suicide pathogenesis, such as serotonin and norepinephrine [50–53]. As demonstrated by our results, where most of the participants had concomitant affective disorders (depression or bipolar disorder) or schizophrenia, patients with suicidal behavior had significantly lower levels of FT3 and TT4, albeit not clinically meaningful, when compared with the control group.

To our knowledge, this is the first systematic review and meta-analysis of available evidence evaluating the relationship between suicide and thyroid function tests. There were some limitations to our study. First, due to the observational nature of all the studies included in this meta-analysis, it was not possible to establish causality. Second, although we used clear and standardized inclusion criteria and comprehensive search strategies, there remains possible sources of bias such as incomplete searching, publication bias, and the influence of confounding factors (current therapies, psychiatric comorbidities, environmental factors, etc.) in our results. Third, there was heterogeneity of the criteria used to define suicide behavior in the included studies (based on clinical records, psychiatric assessment, self-reported, etc.) and the presence of other concomitant psychiatric diseases which can affect the risk of suicidal behavior. Importantly, suicide is a very complex phenomenon related to many mental health diagnoses and with a multitude of biological, psychological, and social variables which should be considered when interpreting our findings.

5. Conclusions

In conclusion, we found that the available evidence regarding the association of hypothyroidism or hyperthyroidism with suicidal behavior is limited. In our best effort to summarize all the available evidence, we have described that patients with suicidal behavior had significantly lower levels of FT3 and TT4 levels compared with controls. However, the data in this field are scarce and have significant heterogeneity. Future large, well conducted studies are needed to increase our confidence in the findings presented here, especially studies reporting the specific association of hypothyroidism/hyperthyroidism in this population, which can provide a better understanding, evaluation, and follow-up of patients with thyroid dysfunction and suicidal behavior.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/medicina57070714/s1. Figure S1, Funnel plots for publication bias analysis; Figure S2, Leave-one-out sensitivity analysis of the studies included; Table S1, Summary of risk of bias assessment for the included studies. File S1: Search Strategies Used in this Project.
Author Contributions: Conceptualization, F.J.K.T., R.O. and S.M.; methodology, F.J.K.T., P.E. and S.M.; paper review and data extraction, F.J.K.T., Y.M., L.M., G.G., M.B. and S.M.; formal analysis, F.J.K.T. and S.M.; writing—original draft preparation, F.J.K.T., H.M., S.T. and S.M.; writing—review and editing, F.J.K.T., Y.M., L.M., G.G., M.B., H.M., S.T., R.O., P.E. and S.M.; funding acquisition, R.O. and S.M. All authors have read and agreed to the published version of the manuscript.

Funding: S.M. receives support by the Arkansas Biosciences Institute, the major research component of the Arkansas Tobacco Settlement Proceeds Act of 2000, and by the United States Department of Veterans Affairs Health Services Research & Development Service of the VA Office of Research and Development, under Merit review award number I121HX003268-01A1. The views expressed in the article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs or the United States Government.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data used in this project are available upon request to contact author.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. WHO. Suicide. 2019. Available online: https://www.who.int/news-room/fact-sheets/detail/suicide (accessed on 10 December 2020).

2. Bachmann, S. Epidemiology of Suicide and the Psychiatric Perspective. Int. J. Environ. Res. Public Health 2018, 15, 1425. [CrossRef] [PubMed]

3. ATA. General Information/Press Room. 2019. Available online: https://www.thyroid.org/media-main/press-room/ (accessed on 10 December 2020).

4. Aoki, Y.; Belin, R.M.; Clickner, R.; Jeffries, R.; Phillips, L.; Mahaffey, K.R. Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999–2002). Thyroid 2007, 17, 1211–1223. [CrossRef] [PubMed]

5. Canaris, G.J.; Manowitz, N.R.; Mayor, G.; Ridgway, E.C. The Colorado Thyroid Disease Prevalence Study. Arch. Intern. Med. 2000, 160, 526–534. [CrossRef]

6. Haskett, R.F. Diagnostic categorization of psychiatric disturbance in Cushing’s syndrome. Am. J. Psychiatry 1985, 142, 911–916. [PubMed]

7. Pivonello, R.; Simeoli, C.; De Martino, M.C.; Cozzolino, A.; De Leo, M.; Jacuaniello, D. Neuropsychiatric disorders in Cushing’s syndrome. Front. Neurosci. 2015, 9, 129. [CrossRef] [PubMed]

8. Walker, M.D.; McMahon, D.J.; Inabnet, W.B.; Lazar, R.M.; Brown, I.; Vardy, S. Neuropsychological features in primary hyperparathyroidism: A prospective study. J. Clin. Endocrinol. Metab. 2009, 94, 1951–1958. [CrossRef] [PubMed]

9. Johns, L.E.; Ferguson, K.K.; Cantonwine, D.E.; Mukherjee, B.; Meeker, J.D.; McLrath, T.F. Subclinical Changes in Maternal Thyroid Function Parameters in Pregnancy and Fetal Growth. J. Clin. Endocrinol. Metab. 2018, 103, 1349–1358. [CrossRef] [PubMed]

10. Heiberg Brix, T.; Ferlov-Schwensen, C.; Thvilum, M.; Hegedus, L. Death by unnatural causes, mainly suicide, is increased in patients with Hashimoto’s thyroiditis. A nationwide Danish register study. Endocrine 2019, 65, 616–622. [CrossRef] [PubMed]

11. Shen, Y.; Wu, F.; Zhou, Y.; Ma, Y.; Huang, X.; Ning, Y.; Lang, X.; Luo, X.; Zhang, X. Association of thyroid dysfunction with suicide attempts in first-episode and drug naïve patients with major depressive disorder. J. Affect. Disord. 2019, 259, 180–185. [CrossRef] [PubMed]

12. Journy, N.M.; Bernier, M.-O.; Doody, M.M.; Alexander, B.H.; Linet, M.S.; Kitahara, C.M. Hyperthyroidism, Hypothyroidism, and Cause-Specific Mortality in a Large Cohort of Women. Thyroid 2017, 27, 1001–1010. [CrossRef]

13. Wells, G.A.; Shea, B.; O’Connell, D.; Peterson, J.; Welch, V.; Losos, M. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies Inmeta-Analyses. 2019. Available online: www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed on 10 December 2020).

14. Cochrane Training. Cochrane Handbook for Systematic Reviews of Interventions: June 2017: Handbook Editors’ Update. 2019. Available online: http://training.cochrane.org/handbook (accessed on 10 December 2020).

15. Egger, M.; Davey Smith, G.; Schneider, M.; Minder, C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997, 315, 629–634. [CrossRef]

16. CLARITY Group at McMaster University. Tools to Assess Risk of Bias in Cohort and Case Control Studies; Randomized Controlled Trials; and Longitudinal Symptom Research Studies Aimed at the General Population. 2013. Available online: http://www.evidencepartners.com/resources/ (accessed on 10 December 2020).
17. Baek, J.H.; Kang, E.S.; Fava, M.; Mischoulon, D.; Nierenberg, A.A.; Yu, B.H. Serum lipids, recent suicide attempt and recent suicide status in patients with major depressive disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 2014, 51, 113–118. [CrossRef]

18. Berlin, I.; Payan, C.; Corruble, E.; Puech, A.J. Serum thyroid-stimulating-hormone concentration as an index of severity of major depression. Int. J. Neuropsychopharmacol. 1999, 2, 105–110. [CrossRef] [PubMed]

19. Berentaitė, B.; Marčuliuniene, A.; Stebilienė, V.; Butkutė-Šluozienė, K.; Adomaitienė, V. WITHDRAWN: P2.016 Thyroid axis functioning in patients with high suicide risk. Eur. Neuropsychopharmacol. 2018, 28, S32–S33. [CrossRef] [PubMed]

20. Duval, F.; Mokrani, M.C.; Lopera, F.G.; Diep, T.S.; Rabia, H.; Fattah, S. Thyroid axis activity and suicidal behavior in depressed patients. Psychoneuroendocrinology 2010, 35, 1045–1054. [CrossRef]

21. Duval, F.; Mokrani, M.C.; Erb, A.; Gonzalez Opera, F.; Calleja, C.; Paris, V. Relationship between chronobiological thyrotropin and prolactin responses to protirelin (TRH) and suicidal behavior in depressed patients. Psychoneuroendocrinology 2017, 85, 100–109. [CrossRef]

22. Jose, J.; Nandeeshha, H.; Kattimani, S.; Meiyappan, K.; Sarkar, S.; Sivasankar, D. Association between prolactin and thyroid hormones with severity of psychopathology and suicide risk in drug free male schizophrenia. Clin. Chim. Acta. 2015, 444, 78–80. [CrossRef] [PubMed]

23. Jokinen, J.; Samuelsson, M.; Nordstrom, A.L.; Nordstrom, P. HPT axis, CSF monoamine metabolites, suicide intent and depression severity in male suicide attempters. J. Affect. Disord. 2008, 111, 119–124. [CrossRef] [PubMed]

24. Krushid, S.; Pervaiz, M.; Akhtar, S.; Elahi, S.; Zaidi, A.; Saeed, Z.; Bukhari, S.M. Changes in thyroid function status of suicidal patients. Arch. Clin. Psychiatry 2018, 45, 12–14. [CrossRef]

25. Kim, B.; Kang, E.-S.; Fava, M.; Mischoulon, D.; Soskin, D.; Yu, B.-H.; Lee, D.; Lee, D.-Y.; Park, H.-D.; Jeon, H.J. Follicle-stimulating hormone (FSH), current suicidal ideation and attempt in female patients with major depressive disorder. Psychiatry Res. 2013, 210, 951–956. [CrossRef]

26. Maes, M.; Vandewoude, M.; Schotte, C.; Martin, M.; Blocks, P.; Scharp, P. Hypothalamic-pituitary-adrenal and -thyroid axis dysfunctions and decrements in the availability of L-tryptophan as biological markers of suicidal ideation in major depressed females. Acta Psychiatri. Scand. 2010, 121, 13–17. [CrossRef]

27. Ozcan, H.; Yucel, A.; Atis, O.; Yucel, N.; Bilen, A.; Emet, M. Thyroxin Levels Associated with Current Suicide Attempts: A Case Control and Follow-Up Study. Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical. Psychopharmacology 2016, 26, 278–286.

28. Pompili, M.; Gibino, S.; Innamorati, M.; Serafini, G.; Del Casale, A.; De Risio, L.; Palermo, M.; Montebovi, F.; Campi, S.; De Luca, V.; et al. Prolactin and thyroid hormone levels are associated with suicide attempts in psychiatric patients. Psychiatry Res. 2012, 200, 389–394. [CrossRef]

29. Peng, R.; Dai, W.; Li, Y. Low serum free thyroxine level is correlated with lipid profile in depressive patients with suicide attempt. Psychiatry Res. 2018, 266, 111–115. [CrossRef]

30. Barbosa, I.; Ferreira, R.; Huguet, R.; Rocha, F.; Salgado, J.; Teixeira, A. Comorbididades clinicas e psiquiátricas em pacientes com transtorno bipolar do tipo I. J. Bras. Psiquiatria 2011, 60, 271–276. [CrossRef]

31. Sanna, L.; Stuart, A.L.; Pasco, J.A.; Kotowicz, M.; Berk, M.; Girardi, P.; Williams, L. Suicidal ideation and physical illness: Does the link lie with depression? J. Affect. Disord. 2014, 152–154, 422–426. [CrossRef] [PubMed]

32. Abraham-Nordling, M.; Lonn, S.; Wallin, G.; Yin, L.; Nyren, O.; Tullgren, O. Hyperthyroidism and suicide: A retrospective cohort study in Sweden. Eur. J. Endocrinol. 2009, 160, 437–441. [CrossRef] [PubMed]

33. Ferlav-Schwensen, C.; Brix, T.H.; Hagedüs, L. Death by Suicide in Graves’ Disease and Graves’ Orbitopathy: A Nationwide Danish Register Study. Thyroid 2017, 27, 1475–1480. [CrossRef]

34. Wang, B.; An, X.; Shi, X.; Zhang, J.-A. Management of Endocrine Disease: Suicide risk in patients with diabetes: A systematic review and meta-analysis. Eur. J. Endocrinol. 2017, 177, R169–R181. [CrossRef]

35. Gradus, J.L.; Qin, P.; Lincoln, A.K.; Miller, M.; Lawler, E.; Sorensen, H.T. Inflammatory bowel disease and completed suicide in Danish adults. Inflamm. Bowel. Dis. 2016, 12, 2518–2561. [CrossRef]

36. Leyhe, T.; Müssig, K. Cognitive and affective dysfunctions in autoimmune thyroiditis. Brain Behav. Immun. 2014, 41, 261–266. [CrossRef] [PubMed]

37. Siegmund, E.M.; Muller, H.H.O.; Luecke, C.; Philipsen, A.; Kornhuber, J.; Gromer, T.W. Association of Depression and Anxiety Disorders With Autoimmune Thyroiditis: A Systematic Review and Meta-analysis. JAMA Psychiatry 2018, 75, 577–584. [CrossRef] [PubMed]

38. Loh, H.H.; Lim, L.L.; Yee, A.; Loh, H.S. Association between subclinical hypothyroidism and depression: An updated systematic review and meta-analysis. BMC Psychiatry 2019, 19, 12. [CrossRef] [PubMed]

39. Fountoulakis, K.N.; Iacovides, A.; Grammaticos, P.; St Kaprinis, G.; Bech, P. Thyroid function in clinical subtypes of major depression: An exploratory study. BMC Psychiatry 2004, 4, 6. [CrossRef]

40. Carta, M.G.; Loviselli, A.; Hardoy, M.C.; Massa, S.; Cadeddu, M.; Sardu, C. The link between thyroid autoimmunity (antithyroid peroxidase autoantibodies) with anxiety and mood disorders in the community: A field of interest for public health in the future. BMC Psychiatry 2004, 4, 25. [CrossRef]

41. Leyhe, T.; Hugle, M.; Gallwitz, B.; Saur, R.; Escheville, G.W. Increased occurrence of severe episodes in elderly depressed patients with elevated anti-thyroid antibody levels. Int. J. Geriatr. Psychiatry 2009, 24, 779–781. [CrossRef]

42. Kupka, R.W.; Nolen, W.A.; Post, R.M.; McElroy, S.L.; Altshuler, L.L.; Denicoff, K.D. High rate of autoimmune thyroiditis in bipolar disorder: Lack of association with lithium exposure. Biol. Psychiatry 2002, 51, 305–311. [CrossRef]
43. Vandoolaeghe, E.; Maes, M.; Vandevyvere, J.; Neels, H. Hypothalamic-pituitary-thyroid-axis function in treatment resistant depression. *J. Affect. Disord.* 1997, 43, 143–150. [CrossRef]

44. Loosen, P.T. Hormones of the hypothalamic-pituitary-thyroid axis: A psychoneuroendocrine perspective. *Pharmacopsychiatry* 1986, 19, 401–415. [CrossRef]

45. Hage, M.P.; Azar, S.T. The Link between Thyroid Function and Depression. *J. Thyroid. Res.* 2012, 2012, 590648. [CrossRef]

46. Garlow, S.J.; Dunlop, B.W.; Ninan, P.T.; Nemeroff, C.B. The combination of triiodothyronine (T3) and sertraline is not superior to sertraline monotherapy in the treatment of major depressive disorder. *J. Psychiatr. Res.* 2012, 46, 1406–1413. [CrossRef]

47. Kelly, T.F.; Lieberman, D.Z. Long term augmentation with T3 in refractory major depression. *J. Affect. Disord.* 2009, 115, 230–233. [CrossRef]

48. Touma, K.T.B.; Zoucha, A.M.; Scarff, J.R. Liothyronine for Depression: A Review and Guidance for Safety Monitoring. *Innov. Clin. Neurosci.* 2017, 14, 24–29. [PubMed]

49. Cooper-Kazaz, R.; Apter, J.T.; Cohen, R.; Karagichev, L.; Muhammed-Moussa, S.; Grupper, D. Combined treatment with sertraline and liothyronine in major depression: A randomized, double-blind, placebo-controlled trial. *Arch. Gen. Psychiatry* 2007, 64, 679–688. [CrossRef] [PubMed]

50. Krishnan, V.; Nestler, E.J. Linking molecules to mood: New insight into the biology of depression. *Am. J. Psychiatry* 2010, 167, 1305–1320. [CrossRef] [PubMed]

51. Brouwer, J.P.; Appelhof, B.C.; Hoogendijk, W.J.; Huyser, J.; Endert, E.; Zuketto, C. Thyroid and adrenal axis in major depression: A controlled study in outpatients. *Eur. J. Endocrinol.* 2005, 152, 185–191. [CrossRef]

52. Duval, F.; Mokrani, M.-C.; Bailey, P.; Correa, H.; Diep, T.-S.; Crocq, M.-A.; Macher, J.-P. Thyroid axis activity and serotonin function in major depressive episode. *Psychoneuroendocrinology* 1999, 24, 695–712. [CrossRef]

53. Jackson, I.M. The Thyroid Axis and Depression. *Thyroid* 1998, 8, 951–956. [CrossRef]