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# The role of psychological factors in predicting infertility treatment success

**PhD thesis**


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# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADH | Adherence |
| ANX | Anxious |
| ART | Assisted Reproductive Technology |
| AT | Affective Temperaments |
| AUC | Area Under the Curve |
| BAASIS | Basel Assessment of Adherence to Immunosuppressive Medication Instrument |
| BMI | Body Mass Index |
| CYC | Cyclothymic |
| CI | Confidence Interval |
| CRS | Clinician Rating Scale |
| DEP | Depressive |
| ET | Exact Test |
| FDR | False Discovery Rate |
| HYP | Hyperthymic |
| ICSI | IntraCytoplasmic Sperm Injection |
| IRR | Irritable |
| IVF | In Vitro Fertilization |
| MARS | Medication Adherence Rating Scale |
| MMAS | Morisky Morisky Medication Adherence Scale |
| OR | Odds Ratio |
| PI | Prediction Interval |
| ROC | Receiver Operating Curve |
| SD | Standard Deviation |
| SDSCA | Summary of Diabetes Self-Care Activities |
| SMD | Standardized Mean Difference |
| TEMPS-A | Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Auto-questionnaire |

# 1. INTRODUCTION

## 1.1. Affective temperaments

### 1.1.1. Definition and clinical importance

Affective temperaments (cyclothymic, depressive, anxious, irritable, and hyperthymic) represent biologically based core traits of personality that emerge early in life and tend to remain stable over time (1). These temperaments influence an individual's baseline mood, level of activity, emotional responses, and typical cognitive patterns. Cyclothymic temperament is typified by rapid mood swings, marked emotional reactivity, and fluctuating self-worth and confidence. Depressive temperament is generally characterized by a persistently low mood, a tendency to adhere to routines and rules, and a heightened sensitivity to criticism and guilt. Anxious temperament involves persistent worry, a tendency to anticipate negative outcomes, and heightened fearfulness, often accompanied by hypervigilance. Individuals with an irritable temperament are more prone to anger and frequent complaints, shaped by the parallel prescence of depressive and hyperthymic traits, which foster skepticism and critical attitudes. Meanwhile, hyperthymic temperament is associated with sociability, elevated confidence, and lower sleep requirements, along with higher energy levels and reduced fatigue.

Unlike the majority of temperament models in psychology that are primarily based on infant research emphasizing normative emotional responses, the affective temperament model stems from clinical and observational studies involving individuals with affective disorders and their unaffected first-degree relatives, and its validity has been confirmed in numerous clinical, theoretical, and biological studies (2-6). While not pathological on their own, affective temperaments represent vulnerability factors for the development of various psychiatric (7, 8) and somatic conditions (9-20), and they may shape the course and treatment outcomes of these illnesses (7, 16, 18, 21). These influences might be exerted either through shared underlying biological mechanisms or indirectly through their impact on emotions, cognitions, and behavioral tendencies, which in turn can affect disease onset or treatment adherence and efficacy (7, 22).

Given the availability of widely validated tools such as the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Auto-questionnaire (TEMPS-A) (23, 24), screening of affective temperaments may be applicable for identifying high-risk subgroups in clinical practice, which ideally could help to approach personalized medicine and enhance cost-effective interventions.

1.1.2. Affective temperaments and treatment outcome

In psychiatry, dominant affective temperaments are frequently viewed as precursors or risk indicators for the emergence of affective disorders, including their subclinical or latent forms (25, 26). Beyond their role in increasing vulnerability to such disorders, affective temperaments are valuable for diagnostic refinement, subtyping of clinical presentations, and forecasting the long-term progression of psychiatric conditions (27). Due to their intrinsic connection to emotional reactivity and a wide range of behavioral and cognitive functions (5), these temperaments are also likely to influence the onset, symptom profile, and chronicity of physical health conditions. Moreover, they may play a pivotal role throughout various stages of medical treatment—including treatment initiation, patient adherence, and ultimate clinical outcomes—given that these stages are shaped by emotional, cognitive, and behavioral mechanisms (16, 28, 29).

There is growing recognition of the relevance of psychological factors in the etiology and management of somatic diseases. This shift aims to identify key psychological targets for intervention to enhance treatment efficacy, improve patients' quality of life, and potentially reduce healthcare costs related to delayed diagnoses, missed prevention opportunities, or treatment failure, including persistent symptoms and adverse side effects. Emerging evidence has highlighted a significant role of affective temperaments in influencing treatment adherence across both psychiatric and somatic health domains (30-38); however, the complex and multidimensional interaction between temperamental traits and the course and outcomes of physical illnesses warrants further exploration to fully harness its clinical potential. A deeper understanding of how affective temperaments shape various aspects of treatment—particularly adherence and outcome—could be especially beneficial in contexts involving elective interventions, which require prolonged commitment, entail strict adherence protocols, and may disrupt daily routines, all while exposing individuals to considerable stress and emotional strain, such as infertility treatments (39).

## 1.2. Adherence

### 1.2.1. Definition and clinical importance

Adherence refers to the extent to which individuals follow medical guidance, encompassing not only the use of prescribed medications but also lifestyle modifications such as dietary changes and physical activity. According to estimates from the World Health Organization (WHO), adherence to long-term therapies for chronic conditions remains suboptimal, with rates in developed countries falling below 50%, and even lower rates reported in developing regions. This insufficient adherence poses a major barrier to achieving optimal therapeutic outcomes and represents a significant public health concern. Poor adherence undermines the effectiveness of treatments, diminishing both individual health outcomes and the broader cost-efficiency of healthcare systems (40).

### 1.2.2. Factors influencing adherence

Adherence to therapy is shaped by a multifaceted interplay of both stable and dynamic influences, involving patient-specific characteristics, treatment-related variables, the quality of the doctor-patient relationship, and broader environmental contexts. Many of these elements are deeply rooted in the patient's psychological profile (41). While structural barriers—such as insufficient psychoeducation, polypharmacy, and infrequent medical follow-ups—are more readily observable, psychological barriers often present greater complexity and are more difficult to detect and manage effectively (42). Among these psychological influences, temperament and personality traits play a significant role, which has been less studied in this context in the past. These traits affect how individuals interpret and respond to treatment through their influence on emotional regulation, cognitive patterns, attitudes, and behavioral tendencies—factors all closely tied to adherence behavior (43).

## 1.3. Infertility

### 1.3.1. Definition and clinical importance

Infertility is a medical condition affecting the reproductive system. According to the World Health Organization (WHO), it is defined as the inability to conceive after at least 12 months of consistent, unprotected sexual intercourse (44). This condition impacts approximately one in six individuals of reproductive age at some point in their lives (44). Moreover, its global prevalence is on the rise (45), which has led to a corresponding increase in the use of assisted reproductive technologies (46).

### 1.3.2. Treatment of infertility

Infertility is associated with several somatic (44), lifestyle-related (47), and psychological contributors (48). Therefore the effective treatment of infertility involves a multifaceted approach that is frequently demanding in terms of cost, duration, and emotional toll (49). Infertility treatment requires a high degree of adherence—not only to pharmacological protocols and medical interventions but also to prescribed lifestyle changes, including dietary adjustments and physical activity routines (50-55). Despite these efforts, the cumulative success rate of infertility treatments remains below 50% (56). Furthermore, the psychological burden of infertility therapies is considerable, with patients commonly experiencing heightened levels of anxiety and depression. These emotional responses are often the result of persistent stress and the cyclical nature of hope and disappointment associated with treatment (57). Consequently, pre-treatment psychological assessment has been recommended to identify individuals who may be more vulnerable to emotional difficulties during the treatment process (58). Nevertheless, in addition to emotional risk screening, assessing the psychological factors that contribute to treatment non-adherence is equally vital. This is underscored by findings indicating that adherence to prescribed medications during infertility treatment is approximately 50% (51), and compliance with lifestyle modification guidance is also frequently lacking (50-55). Such low adherence rates pose a significant challenge to the overall efficacy of infertility interventions.

### 1.3.3. Affective temperaments and infertility treatment success

Affective temperaments may play a significant role in determining the effectiveness of infertility treatment through multiple, partially interrelated mechanisms. These temperamental traits can influence an individual's psychological status, adherence to therapeutic protocols and necessary lifestyle modifications, and several other behaviors and cognitions —factors that collectively contribute to the overall success of infertility treatment, particularly within the context of assisted reproductive technologies. Given these associations, affective temperaments may have a contributory role in the outcome of infertility treatments via both screening for high-risk patient groups and predicting the likelihood of treatment success, as well as tailoring and personalizing treatment. Although these temperament traits are biologically grounded and relatively stable over the course of a person’s life, they may still offer insight into behavioral pathways that can be adjusted to improve treatment efficacy. Despite a growing number of literature highlighting the relevance of affective temperaments in various somatic conditions and their treatment outcomes, their specific influence on infertility treatment success has not yet been explored.

# 2. OBJECTIVES

Our studies aimed to investigate the impact of psychological factors on infertility treatment success. Specifically, to investigate whether affective temperaments affect treatment adherence and, through adherence, the outcome of infertility treatment among female patients attempting assisted reproduction.

To find the answer to the above questions, our specific objectives were:

1) To investigate the effect of affective temperaments on treatment adherence using a systematic review and meta-analytic approach.

2) To investigate the impact of affective temperaments on infertility treatment outcomes among women attempting assisted reproduction.

3) To evaluate whether adherence to physician-prescribed diet and physical activity recommendations mediates the effect of affective temperaments on infertility treatment outcomes.

# 3. METHODS

## 3.1. Study 1: Affective temperaments on adherence

### 3.1.1. Search strategy

A comprehensive literature search was conducted across Scopus, Web of Science, PubMed, and OVID MedLine databases from inception through March 31, 2022. The search employed the keywords: “TEMPS-A” in combination with either “adherence” or “compliance.” To ensure completeness, the initial database queries were supplemented with manual searches and cross-references validation.

### 3.1.2. Study selection

Following the initial database search, all identified records were compiled and screened for duplicates, which were subsequently removed. No restrictions were placed regarding study design, participant age, type of treatment, or language of publication. Due to the inclusion of the term “TEMPS-A” in our search criteria, no qualitative studies were retrieved. Studies were eligible for inclusion if they reported quantitative data on individual affective temperament dimensions assessed using the TEMPS-A instrument, alongside treatment adherence or compliance measured by any standardized adherence tool. To permit effect size analysis, studies also needed to report associations between TEMPS-A scores and adherence outcomes, such as correlation coefficients or mean differences.

### 3.1.3. Data extraction and analysis

Data from all eligible studies were systematically extracted, including information on the country of origin, patient population characteristics (e.g., sample size, age distribution, gender ratio, and type of clinical population), instruments used to assess affective temperaments, and methods and tools applied to measure adherence. We also collected the mean scores and standard deviations (SDs) of each temperament subscale for both adherent and non-adherent groups, or alternatively, the correlation coefficients between temperament dimensions and adherence levels. In cases where both mean comparisons and correlations were available, we prioritized correlation data to reduce variability introduced by arbitrary adherence thresholds used to define group membership. For studies that presented multiple adherence subgroups or stratified means (e.g., by gender), data were aggregated using weighted means and pooled SDs. All extracted values were transformed into standardized mean differences (SMDs) and corresponding SDs to facilitate meta-analytic synthesis. Given the anticipated methodological variability across studies—particularly in the tools used to assess adherence—a random-effects model was employed for pooling SMDs between adherent and non-adherent participants. Results are reported as pooled SMDs along with 95% confidence intervals (CIs).

To quantify between-study heterogeneity, prediction intervals were calculated to estimate the distribution of true effects. Additional heterogeneity statistics included the Q-statistic (assessing whether all studies share a common effect size), $I^2$ (representing the percentage of total variance attributable to heterogeneity rather than sampling error), and $Tau^2$ (reflecting the variance among true effect sizes) (59). Potential sources of heterogeneity were examined through visual inspection of forest plots for outliers and via subgroup analyses.

Quality and risk of bias within studies were evaluated using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (60). To assess potential publication bias, funnel plots were generated and statistically tested using Begg and Mazumdar's rank correlation and Egger's regression test. Sensitivity analysis was conducted to examine the influence of individual studies on overall results.

All statistical analyses were implemented using the R package metaphor v.3.0 (61).

## 3.2. Study 2: Affective temperaments on infertility treatment outcomes

### 3.2.1. Study population

Between November 2019 and November 2021, a total of 1,773 Hungarian women who scheduled their initial visit at the Assisted Reproduction Centre of the Department of Obstetrics and Gynecology at Semmelweis University in Budapest were retrospectively contacted via email in November 2022. Of these, 593 individuals consented to participate, 18 declined, and 1,162 did not reply, resulting in an overall participation rate of 34.5%.

Eligibility criteria included women aged 18 to 45 at the time of their first appointment—aligned with the national guidelines for assisted reproduction in Hungary—who had been attempting to conceive for at least one year within the prior three years. Additional criteria required fluency in Hungarian, willingness to take part in the research, completion of the study questionnaire, and the provision of informed consent.

Exclusion criteria encompassed those undergoing fertility preservation in anticipation of cancer treatment, cases solely due to male but not female infertility, and individuals seeking assisted reproduction services without the intention to conceive. The number of prior pregnancies (natural or assisted) and existing children did not affect eligibility. Apart from these specific conditions, standard criteria for inclusion and exclusion in assisted reproduction protocols were applied.

After eliminating duplicate and invalid responses, a total of 578 participants formed the final study cohort. Information related to demographics, body measurements, psychological assessments, and medical history was gathered either through self-reported questionnaires or extracted from clinical records. All participants provided written consent to allow data collection and analysis. The research protocol received approval from the Scientific and Research Ethics Committee of the Medical Research Council under the Hungarian Ministry of Health (IV/1568-1/2022/EKU) and was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki.

### 3.2.2. Evaluation of affective temperaments

Affective temperaments were measured using the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego (TEMPS-A) auto-questionnaire. TEMPS-A is a 110-item self-report instrument developed to assess affective temperaments in cyclothymic, depressive, anxious, irritable, and hyperthymic subscales, requiring "yes" (score 1) or "no" (score 0) answers (24, 62). The questionnaire showed good to excellent internal reliability of the scales in the Hungarian normative population in the validation study (62): depressive (21 items, Cronbach's alpha = 0.63); cyclothymic (21 items; Cronbach's alpha = 0.81); irritable (seven items; Cronbach's alpha = 0.79); anxious (26 items; Cronbach's alpha = 0.84); and hyperthymic (21 items; Cronbach's alpha = 0.78). In the current sample, very similar or better internal reliability of the scales was confirmed: depressive (21 items, Cronbach's alpha = 0.66); cyclothymic (21 items; Cronbach's alpha = 0.83); irritable (seven items; Cronbach's alpha = 0.80); anxious (26 items; Cronbach's alpha = 0.86); and hyperthymic (21 items; Cronbach's alpha = 0.77).

3.2.3. Assisted reproduction techniques

The techniques used were heterogeneous based on each patient's clinical situation and fertility diagnosis. In most cases, treatment involved ovarian stimulation protocols (63), followed by either traditional in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI). When indicated, these were supplemented by oral medications or additional therapies addressing specific infertility-related conditions. Due to the heterogeneity of the protocols and the fact that, according to a comprehensive meta-analysis, particular techniques have not been found to be predictors of treatment outcome (64), infertility treatment was considered a constant in this study.

3.2.4. Evaluation of treatment success

Infertility treatment success was defined as clinical pregnancy (confirmed by ultrasound with the presence of an amniotic sac, embryo, and fetal heartbeat) following infertility treatment, as reported by the patients.

3.2.5. Evaluation of potential covariates

Patient age at the initial consultation was calculated using the date of birth and the date of the first appointment. Body mass index (BMI) at the first visit was extracted from clinical records. Additional variables, including history of miscarriage, as well as physical and mental health diagnoses, were self-reported by the patients.

3.2.6. Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) and range; categorical variables are expressed as numbers and percentages. Between-group differences in descriptive characteristics and TEMPS-A scores were detected using the Wilcoxon rank sum test for continuous variables and Pearson's Chi-squared test or

Fisher's exact test (applied when expected frequencies were ≤ 5) for categorical values. TEMPS-A scores were compared to the normative population average using one-sample Wilcoxon signed rank test. To correct for multiple comparisons in each univariate analysis, Benjamini–Hochberg false discovery rate (FDR) adjusted p-values (q-values) were calculated. Calculating with a 5% false discovery rate results with a q-value < 0.05 were considered significant.

Multivariate logistic regression analysis was used to determine the relationship between affective temperaments and infertility treatment success with all possible other predictors as covariates. Due to the high degree of intercorrelation between affective temperaments, they were fitted into the multiple regression analyses separately. The predictive power of affective temperaments was initially investigated as continuous variables. Thereafter, receiver operating curve (ROC) analysis was performed, and optimal cut-off values were defined based on the Youden index (sensitivity + specificity minus 1) for affective temperament scores in each of the five subscales. The results are presented as odds ratios (OR) and 95% confidence intervals (CI). The nominal significance threshold was $p < 0.05$ in all analyses. All calculations were performed using R Statistical Software (Vienna, Austria version 4.2.2).

### 3.2.7. Sample size estimation

A statistical power analysis was performed using the G Power program to estimate the sample size (65). With a small effect size (OR=0.5), alpha of 0.05, and power of 0.95, the projected minimum sample size needed in logistic regression analysis was 129 when calculating with continuous predictors and 378 when calculating with binary predictors.

## 3.3. Study 3: Adherence as a mediator of affective temperaments on infertility treatment outcomes

### 3.3.1. Study population

In this study, the same population participated as in the previous one, expanded with an extra inclusion criterion: the doctor's recommendation of having diet and regular physical activity as part of their treatment so that adherence can be interpreted and evaluated. Of the 578 patients presented in the previous study, 308 had both diet and sports recommendations in their treatment plan, so they were included in this study.

3.3.2. Evaluation of adherence

While all patients who received dietary and exercise guidance from their physician exhibited some form of metabolic irregularity—either diagnosed or subclinical—the specific conditions varied, resulting in a non-uniform set of recommendations. Consequently, dietary and physical activity plans were tailored to the individual, necessitating a personalized approach to evaluating adherence. Typically, dietary recommendations involved a customized plan detailing daily or per-meal carbohydrate intake, developed in consultation with a dietitian. Physical activity guidelines generally consisted of engaging in moderate-intensity exercise for at least 40 minutes, 3 to 5 times per week. To assess adherence to these individualized regimens, the gap between prescribed and actual behaviors was examined. Information about whether dietary and exercise recommendations were provided was obtained from both self-reports and patients' medical records.

Diet and physical activity adherence was evaluated using a modified 7-point Likert scale derived from the Summary of Diabetes Self-Care Activities (SDSCA) questionnaire (66), adapted for retrospective setting. For dietary adherence, patients were first asked whether their physician had recommended a specific diet or meal plan during their fertility treatment. If so, they were then asked how many days per week, on average, they had followed this plan. Patients were categorized as adherent if they reported following the recommended dietary plan every day of the week.

Regarding adherence to exercise recommendations, patients were asked if their physician had advised them to engage in regular physical activity during treatment. Those who answered affirmatively were further asked how many days per week their doctor recommended exercise and how many days, on average, they managed to meet this goal. Patients were classified as adherent if they reported matching or exceeding the recommended number of weekly sessions.

Importantly, individuals who denied receiving dietary or physical activity guidance, despite documentation in their clinical records indicating otherwise, were classified as non-adherent.

### 3.3.3. Statistical analysis

Of the 578 patients presented in our previous study, 308 had dietary and sports recommendations in their treatment plan, so they were included in this current study. The main characteristics of this subgroup of 308 patients were compared with the entire population of 578 patients using the Wilcoxon rank sum test for continuous variables and Pearson's Chi-squared test for categorical values. Relying on the similarity of the two populations, in this analysis, we work with the previously identified covariates; the other examined variables are not reported here again. Continuous variables are expressed as mean ± standard deviation (SD) and range; categorical variables are expressed as numbers and percentages. Between-group differences in descriptive characteristics were detected using the Wilcoxon rank sum test for continuous variables and Pearson's Chi-squared test for categorical values. Univariate linear regression analyses were performed to examine the relationship between infertility treatment success as the response variable and diet or sport adherence as possible predictor variables. Both models were adjusted for age, BMI, and previous miscarriage as already known confounders. After that, causal mediation analysis was applied to examine whether any of the adherence variables that significantly predicted infertility treatment success based on the univariate analysis mediates the effect of affective temperaments on infertility treatment success. Causal mediation analysis was run with affective temperaments as exposure, infertility treatment success (clinical pregnancy) as response, and adherence as mediator variables, also adjusted for age, BMI, and previous miscarriage. The results are presented as odds ratios (OR) and 95% confidence intervals (CI). The significance threshold was set to $p < 0.05$ in all analyses. All calculations were performed using R Statistical Software (Vienna, Austria version 4.2.2).

### 3.3.4. Sample size estimation

Since power estimation tools are lacking for mediation analysis, we used published empirical guidelines to determine the sample size necessary to conduct mediational studies with an 80% statistical power (67). Calculating with medium effect sizes for exposure on mediator and mediator on outcome, with an alpha of 0.05 and power of 80%, the suggested minimum sample size range needed was between 116 and 178.

# 4. RESULTS

## 4.1. Study 1: Affective temperaments on adherence

### 4.1.1. Descriptive statistics

The adopted search strategy returned a total of 219 hits, resulting in 169 records after duplicate removal, which were screened on title and abstract for inclusion criteria, out of which 147 were excluded for not providing the required information. Twenty-two records were ultimately selected for detailed review and potential inclusion. In one of the identified studies, necessary data was only partially reported, but successful contact with the authors allowed for including that record (31).

Ten publications were eligible for meta-analytic synthesis (30-38, 68). However, one record was ultimately disregarded since its adherence definition (treatment drop-out) significantly differed from the rest of the other included studies (medication adherence). Finally, nine records encompassing 1138 subjects effectively participated in the evidence's meta-analytic synthesis (Figure 1, Table 1).

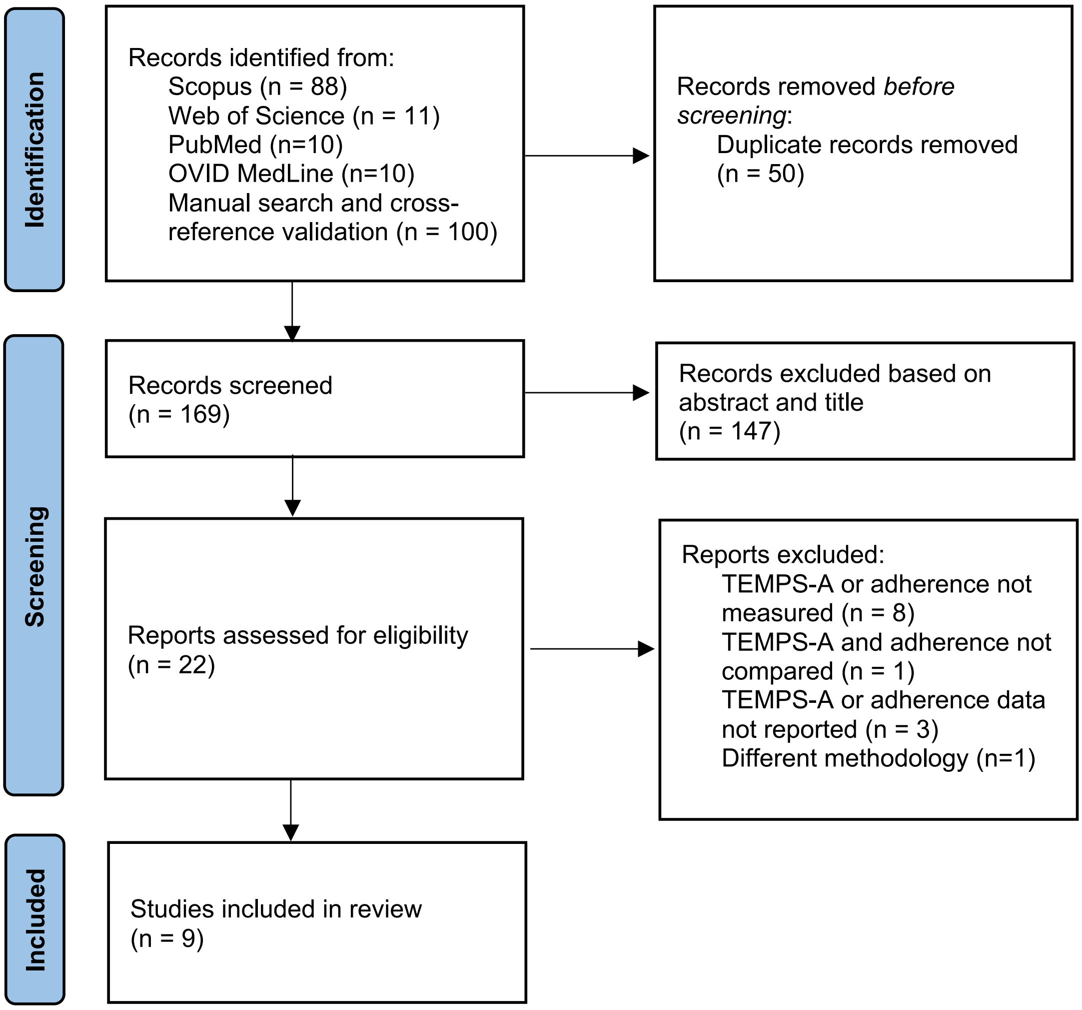


**Figure 1. PRISMA flowchart.** Flowchart of study identification and selection process (29).

The core characteristics of the nine analyzed reports (30-38) appear in Table 1. All studies found significant associations between adherence and TEMPS-A scores for one or more of cyclothymic, depressive, anxious, irritable, or hyperthymic temperament across four psychiatric and five non-psychiatric samples. TEMPS-A subscale scores were higher among non-adherent versus adherent subjects as follows: irritable (k=8 out 9=89%), cyclothymic (k=6 out 9=67%), depressive (k=6 out 9=67%), anxious (k=3 out 9=33%), hyperthymic (k=1 out 9=11%).

**Table 1.** Characteristics of the included studies (29).

| Study | Subjects | Country | Age (mean) | Sex (f%) | Population | Affetive temperaments [scale] | Adherence [scale] | Statistics used | Adh-AT related findings | Study quality |
|---|---|---|---|---|---|---|---|---|---|---|
| Belvederi Murri et al., 2017 | 279 | Italy | 57.45 | 48.02 | Non-psychiatric (Diabetes type 1 and 2) | TEMPS-A-39 [Z-score] | MMAS-4 [0-4] high score: low adh | correlation | irr - low adh<br>dep - low adh<br>cyc - low adh | I |
| Bahrini et al., 2015 | 36 | Tunisia | 37 | 33.3 | Psychiatric (various) | TEMPS-A (lebanese) [0,25] | MARS (medication adh scale) [1-4] high score: high adh | correlation | irr - low adh<br>dep - low adh | II |
| Kamei et al., 2013 | 38 | Japan | 52.2 | 39.47 | Psychiatric (various) | TEMPS-A [1,2] | VAS (medication adh scale) [0-100] high score: high adherence | correlation | irr - low adh | II |
| Fornaro et al., 2013 | 220 | Italy | 38.95 | 58.63 | Psychiatric (Bipolar Depression type II) | TEMPS-A (rome) [0,25] | MMAS-8 + CRS (combined) [0-8] high score: high adherence | mean difference (cut point: 5) | cyc - low adh<br>irr - low adh<br>dep - low adh<br>anx - low adh<br>hyp - low adh | I |
| Shamsi et al., 2014 | 207 | Iran | 48.4 | 61.8 | Non-psychiatric (Diabetes type 2) | TEMPS-A [1,2] | Likert scale [1-5] high score: high adherence | mean difference (cut point: 4) | cyc - low adh<br>irr - low adh<br>dep - low adh<br>anx - low adh | I |
| Shamsi et al., 2021 | 150 | Iran | 48.48 | 54.66 | Non-psychiatric (Congestive Heart Failure) | TEMPS-A-35 [0,1] | MMAS-8 [0-8] high score: high adherence | mean difference (cut point: 6) | irr - low adh | I |
| Yamamoto et al., 2021 | 54 | Japan | 58.94 | 43.89 | Non-psychiatric (Diabetes type 2) | TEMPS-A [Z-score] | MMAS-4 [0-4] high score: low adherence | correlation<br>mean difference (cut point: 2) | cyc - low adh | I |
| Buturak et al., 2016 | 80 | Turkey | 40.74 | 57.5 | Psychiatric (Bipolar Depression type I) | TEMPS-A (turkish) [0,25] | MMAS-4 [0-4] high score: low adherence | correlation<br>mean difference (cut point: 1) | cyc - low adh<br>irr - low adh<br>dep - low adh<br>anx - low adh | II |
| Pasquale et al., 2016 | 74 | Italy | 48.3 | 42.25 | Non-psychiatric (Kidney transplant) | TEMPS-A [0,1] | BAASIS ('taking' scale) [0,5] high score: low adherence | correlation | cyc - low adh<br>irr - low adh<br>dep - low adh | I |
| **Totals (k=9)** | **1138** | **5 countries** | | | **Psychiatric (4)<br>Non-psychiatric (5)** | **TEMPS-A (7)<br>TEMPS-A short (2)** | **Various scales, all addressing medication adh** | **Correlation (4)<br>Mean difference (3)<br>Both (2)** | **6/9 (67%) cyc - low adh<br>8/9 (89%) irr - low adh<br>6/9 (67%) dep - low adh<br>3/9 (33%) anx - low adh<br>1/9 (11%) hyp - low adh** | |

TEMPS-A:Temperament Evaluation of Memphis, Pisa, Paris and San Diego–autoquestionnaire version; MMAS: Morisky Morisky Medication Adherence Scale; MARS: Medication Adherence Rating Scale; CRS: Clinician Rating Scale, an ordinal scale of 1–7 to quantify the clinician's assessment of the level of adherence; BAASIS: Basel Assessment of Adherence to Immunosuppressive Medication instrument, cyc: cyclothymic; irr: irritable; dep: depressive; anx: anxious; hyp: hyperthymic; adh: adherence; AT: affective temperaments; Study quality: II: good, I: potential risks identified, 0:poor, based on JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies

4.1.2. Quality and risk of bias within studies

The risk of bias within studies was assessed using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (60). According to our assessment, we identified potential risks of bias in seven studies (30-35, 37) due to using non-validated scales, applying the non-standardized definition of cut-points used to dichotomize adherence scales into adherent and non-adherent groups, or potential imprecision in reported data.

4.1.3. Meta-analysis

Quantitative analysis was performed for each affective temperament type to test for differences in TEMPS-A subscale scores between adherent and non-adherent subjects. A negative effect represents that subjects with higher TEMPS-A scores favor lower adherence. All results are detailed in Table 2, and those of particular interest are summarized below.

**Table 2.** Summary of meta-analyses of TEMPS-A ratings associated with adherence (29).

| Temperament | Sample size (n) | | Effect size (pooled SMD) | | Test of null | | Heterogeneity | | | True effect size | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Studies | Subjects | SMD | (95% CI) | Z | p(Z) | Q | p(Q) | I2 | Tau2 | (95% PI) |
| Cyclothymic | 9 | 1138 | **-0.869** | ( -1.54 to -0.2 ) | -2.54 | **0.011** | 157.21 | **0.000** | **95.52** | 0.99 | ( -2.93 to 1.19 ) |
| Irritable | 9 | 1138 | **-0.772** | ( -1.14 to -0.4 ) | -4.11 | **0.000** | 64.20 | **0.000** | **85.65** | 0.26 | ( -1.84 to 0.29 ) |
| Depressive | 9 | 1138 | **-0.756** | ( -1.39 to -0.12 ) | -2.34 | **0.019** | 154.19 | **0.000** | **95.14** | 0.88 | ( -2.7 to 1.19 ) |
| Anxious | 9 | 1138 | -0.248 | ( -0.52 to 0.02 ) | -1.80 | 0.072 | 29.47 | 0.000 | 74.38 | 0.12 | ( -0.97 to 0.48 ) |
| Hyperthymic | 9 | 1138 | 0.045 | ( -0.34 to 0.43 ) | 0.23 | 0.817 | 44.21 | 0.000 | 87.18 | 0.28 | ( -1.06 to 1.15 ) |

Based on standardized mean differences (SMD) in TEMPS-A scores in random-effects meta-analysis. CI: confidence interval, tells us how precisely we have estimated the mean effect; Z-statistic: test of the null hypothesis that effect size is zero, rejected if p<0.05; Q-statistic: test of the null hypothesis that all studies in the analysis share a common effect size, rejected if p<0.05; $I^2$: percentage of the variance in observed effects reflects variance in true effects rather than sampling error; $Tau^2$: the variance of the true effects sizes; PI:prediction interval, tells us how the true effect size varies across populations.

Based on nine studies meeting inclusion criteria (total n=1138 subjects), patients with lower adherence had significantly higher cyclothymic (SMD= -0.869, CI: [-1.54 to -0.2], p=0.011), irritable (SMD= -0.772 [CI: -1.14 to -0.4], p<0.001) and depressive (SMD = -0.756, CI: [-1.39 to -0.12], p=0.019) TEMPS-A scores compared to adherent subjects. Anxious (p=0.072) and hyperthymic (p=0.817) TEMPS scores were not different between the two groups.

Heterogeneity was high for all temperaments subscales ($I^2$=88-95%, p<.001), with wide prediction intervals for the true effect size estimation, including zero, suggesting that true effects vary from around -2.9 SMD in some populations to 1.2 SMD in others.

Forest plots with pooled SMDs, 95% CI-s, and 95% prediction intervals (PI-s) for the relevant temperament subscales (where statistically significant associations of affective temperament scores with adherence were found) are presented in Figure 2.

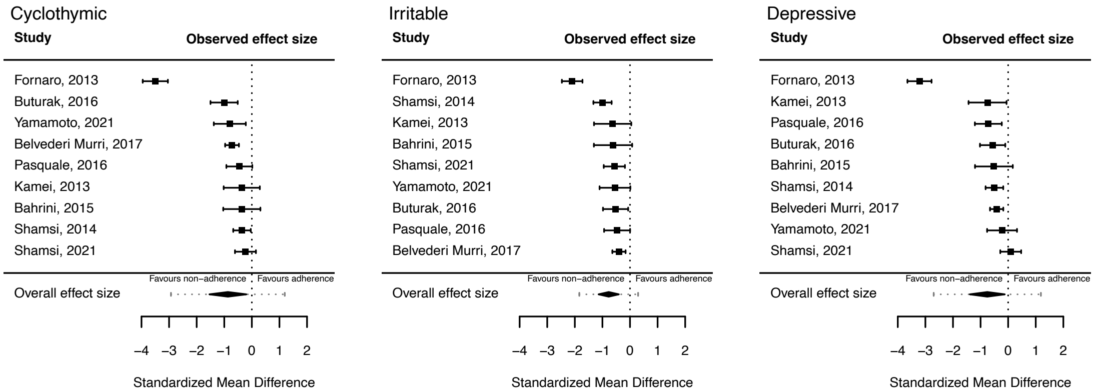


**Figure 2. Meta-analysis of studies investigating the effect of affective temperaments on medication adherence.** Forest plots based on random- effects meta-analyses of TEMPS-A scores for cyclothymic, irritable, and depressive temperaments with 95% confidence intervals (CIs) in nine comparisons of adherent versus non-adherent subjects (total n = 1138), with pooled standardized mean differences (SMDs). The estimated 95% prediction interval (PI) was likewise presented, in which the true effect size was predicted to fall in 95% of all comparable populations (29).

4.1.4. Sensitivity analysis

*4.1.4.1. Impact of one outlying study*

Inspecting the forest plots (Figure 2) revealed one outlying study (35), which reported a much bigger effect size than the rest of the others. Meta-analysis was repeated, with the latter study excluded. The main findings of the meta-analysis without the one outlier study are summarized in Table 3.

**Table 3.** Summary of meta-analyses of TEMPS-A ratings associated with adherence (one outlier removed) (29).

| Temperament | Sample size (n) | | Effect size (pooled SMD) | | Test of null | | Heterogeneity | | | True effect size | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Studies | Subjects | SMD | (95% CI) | Z | p(Z) | Q | p(Q) | I2 | Tau2 | (95% PI) |
| Cyclothymic | 8 | 918 | **-0.538** | ( -0.73 to -0.35 ) | -5.48 | **0.000** | 10.59 | 0.157 | 36.61 | 0.03 | ( -0.91 to -0.17 ) |
| Irritable | 8 | 918 | **-0.591** | ( -0.78 to -0.41 ) | -6.29 | **0.000** | 8.60 | 0.283 | 32.45 | 0.02 | ( -0.93 to -0.25 ) |
| Depressive | 8 | 918 | **-0.414** | ( -0.61 to -0.22 ) | -4.25 | **0.000** | 10.52 | 0.161 | 37.25 | 0.03 | ( -0.79 to -0.04 ) |
| Anxious | 8 | 918 | -0.192 | ( -0.48 to 0.09 ) | -1.31 | 0.189 | 23.07 | 0.002 | 72.25 | 0.11 | ( -0.92 to 0.53 ) |
| Hyperthymic | 8 | 918 | 0.042 | ( -0.1 to 0.18 ) | 0.59 | 0.557 | 17.59 | 0.014 | 0.00 | 0.00 | ( -0.1 to 0.18 ) |

Based on standardized mean differences (SMD) in TEMPS-A scores in random-effects meta-analysis. CI: confidence interval, tells us how precisely we have estimated the mean effect; Z-statistic: test of the null hypothesis that effect size is zero, rejected if p<0.05; Q-statistic: test of the null hypothesis that all studies in the analysis share a common effect size, rejected if p<0.05; $I^2$: percentage of the variance in observed effects reflects variance in true effects rather than sampling error; $Tau^2$: the variance of the true effects sizes; PI:prediction interval, tells us how the true effect size varies across populations.

The exclusion of the outlying study from the meta-analysis resulted in a still large sample (k=8, n=918), insignificant heterogeneity ($I^2$=32-37%, p>.05), and a somewhat reduced but still significant negative meta-analytic association for cyclothymic, irritable and depressive temperaments. Estimated PI-s no longer include zero, suggesting that a negative true effect exists in 95% of all comparable populations.

Forest plots without the one outlier study with pooled SMDs, 95% CI-s, and 95% prediction intervals for the relevant temperament subscales are presented in Figure 3.

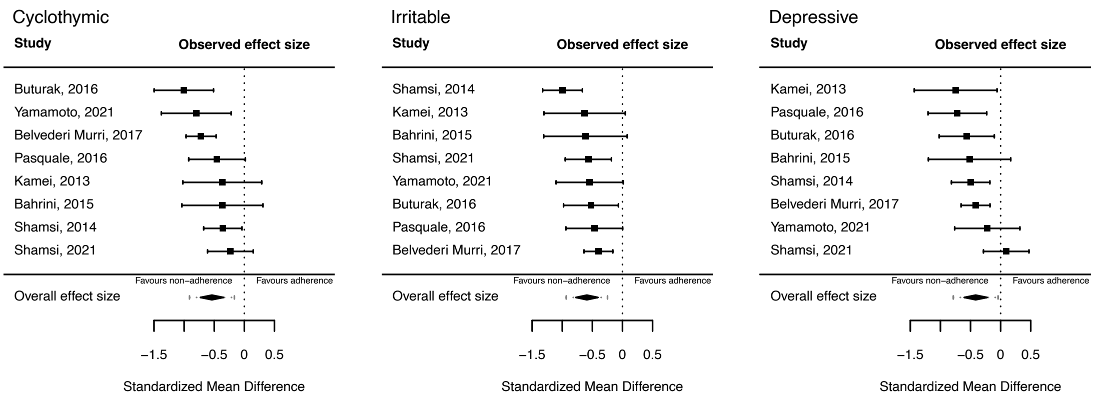


**Figure 3. Meta-analysis of studies investigating the effect of affective temperaments on medication adherence (one outlier removed).** Forest plots without the one excluded study, based on random-effects meta-analyses of TEMPSA scores for cyclothymic, irritable, and depressive temperaments with 95% CIs in eight comparisons of adherent versus non-adherent subjects (total n = 918), with pooled SMDs. The

estimated 95% PIs also displayed, in which the true effect size was predicted to fall in 95% of all comparable populations (29).

*4.1.4.2. Impact of individual studies*

To investigate the impact of each individual study on the summary estimate, sensitivity analysis was performed by iteratively excluding one study from the analyses and recalculating the overall SMDs. We conducted analyses with and without the excluded outlying study to ensure its removal didn't cause bias. The overall SMDs did not vary substantially after excluding any individual study, indicating that the results were not driven by one of the analyzed individual studies either with or without the excluded outlying study.

4.1.5. Publication Bias

Publication bias analysis was performed on eight studies after removing one outlier (30-34, 36-38). Based on inspection of funnel plots, and also on Egger's regression and Begg and Mazumdar's rank correlation tests (p=0.976; 0.933; 0.497, and p=1.000; 0.548; 0.398 for cyclothymic/ irritable/ depressive TEMPS-A subscales, respectively), there was no evidence of publication bias (Figure 4).

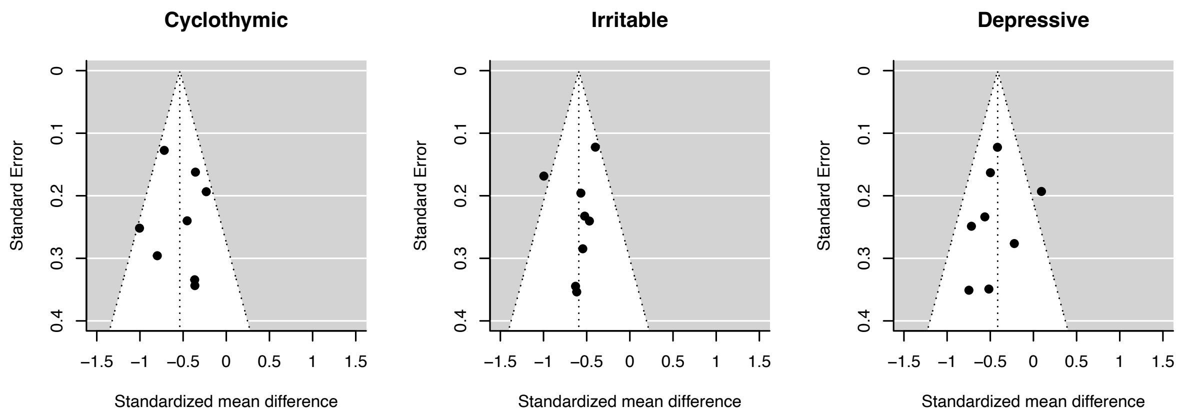


**Figure 4. Funnel plot of the studies included in the comparison of (relevant) TEMPS-A subscale scores and adherence (29)**.

## 4.2. Study 2: Affective temperaments on infertility treatment outcomes

### 4.2.1. Descriptive statistics

In total, our retrospective cohort study included 578 women (22–46 years of age) who underwent infertility treatment in the Assisted Reproduction Centre of the Department of Obstetrics and Gynecology of Semmelweis University in Budapest, Hungary, between November 2019 and November 2021. 366 (63%) of the participants were primarily infertile, 84 (15%) already had at least one child from a previous pregnancy, while 128 (22%) did not have children yet but had already achieved getting pregnant, which ended in miscarriage(s). The mean age of our cohort was 35.78 ± 4.74 years, and the mean BMI was 24.24 ± 4.90 kg/m$^2$. In terms of affective temperaments, the current infertile population differed from the average obtained in the otherwise smaller normative sample (n=438), as the cyclothymic, anxious, and irritable average scores were significantly lower than the Hungarian female population average examined by Rozsa et al. (4.43±3.94 vs 7.98 (W=21618, q=0.005), 7.21±5.22 vs 8.06 (W=60484, q=0.005), and 4.02±3.52 vs 5.88 (W=38927, q=0.005), respectively) (62). Depressive and hyperthymic average scores were not significantly different compared to the population mean (7.3±3.03 vs 7.35 (W=79754, q=0.486), and 10.15±4.04 vs 10.29 (W=81423, q=0.700), respectively).

The probable causes of infertility were highly variable among the patients, the most typical of which included various problems of carbohydrate metabolism (42%), thyroid function problems (36%), endometriosis (10%), or a combination of these, while in case of 51% of the patients there was no identifiable disease behind infertility. The applied assisted reproduction treatments were also diverse. In most cases, ovarian stimulation was applied according to one of the standard protocols (63), followed by either traditional in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI), supplemented as necessary with medications or other kinds of treatment for the presumed problems behind the infertility. The applied infertility treatment resulted in clinical pregnancy in 225 out of 578 cases (39%).

The mean age of patients who successfully became pregnant after the treatment was approximately two years less than those who failed to conceive after treatment (34.43 ± 4.47 vs 36.65 ± 4.72 years (W=50414, $q$ = 0.005)). No statistically significant difference could be observed regarding BMI, socio-economic parameters such as education or residence, nor regarding clinical history parameters such as previous pregnancy, miscarriage, live birth, known psychiatric or somatic illnesses, or the time since being diagnosed with infertility.

Regarding affective temperaments, the mean score of cyclothymic and anxious temperaments proved to be significantly lower in the pregnant cohort compared to the non-pregnant one ($3.80 \pm 3.64$ vs $4.83 \pm 4.08$ points (W=45689, $q = 0.008$) and $6.45 \pm 4.81$ vs $7.69 \pm 5.42$ points (W=44772, $q = 0.035$), respectively). Demographic parameters, clinical data, and scores in the different scales of affective temperaments are summarized in Table 4.

**Table 4.** Demographic parameters, infertility risk factors, and TEMPS-A scores of patients with successful and unsuccessful infertility treatment (69).

| **Characteristics** | | **Treatment success (clinical pregnancy)** | | | | |
|---|---|---|---|---|---|---|
| | **Total** | **(-)** | **(+)** | **Test statistic** | **p-value** | **q-value** |
| **Number** | 578 | 353 (61%) | 225 (39%) | - | - | - |
| **Age (years)** | 35.78 (4.74) [22.00, 46.00] | **36.65 (4.72) [22.00, 45.00]** | **34.43 (4.47) [24.00, 46.00]** | W=50414 | <0.001 | **0.005** |
| **BMI (kg/m2)** | 24.24 (4.90) [16.50, 55.60] | 24.61 (5.24) [16.50, 55.60] | 23.66 (4.27) [17.00, 42.40] | W=43276 | 0.069 | 0.149 |
| *Affective temperaments* | | | | | | |
| **Cyclothymic** | 4.43 (3.94) [0.00, 19.00] | **4.83 (4.08) [0.00, 18.00]** | **3.80 (3.64) [0.00, 19.00]** | W=45689 | 0.002 | **0.008** |
| **Depressive** | 7.30 (3.03) [0.00, 19.00] | 7.56 (3.12) [0.00, 19.00] | 6.89 (2.83) [0.00, 18.00] | W=44120 | 0.024 | 0.075 |
| **Anxious** | 7.21 (5.22) [0.00, 23.00] | **7.69 (5.42) [0.00, 23.00]** | **6.45 (4.81) [0.00, 22.00]** | W=44772 | 0.01 | **0.035** |
| **Irritable** | 4.02 (3.52) [0.00, 16.00] | 4.03 (3.47) [0.00, 16.00] | 4.00 (3.61) [0.00, 16.00] | W=40524 | 0.7 | 0.754 |
| **Hyperthymic** | 10.15 (4.04) [0.00, 21.00] | 9.89 (4.05) [0.00, 21.00] | 10.55 (3.99) [0.00, 20.00] | W=35964 | 0.055 | 0.128 |
| *Clinical history* | | | | | | |
| **Infertile for (years)** | | | | $\chi^2$=3.2 | 0.075 | 0.150 |
| <2 | 302 (52%) | 174 (49%) | 128 (57%) | | | |
| >2 | 276 (48%) | 179 (51%) | 97 (43%) | | | |
| **Previous pregnancy** | 212 (37%) | 127 (36%) | 85 (38%) | $\chi^2$=0.19 | 0.7 | 0.754 |
| **Previous miscarriage** | 197 (34%) | 114 (32%) | 83 (37%) | $\chi^2$=1.3 | 0.3 | 0.467 |
| **Previous live birth** | 84 (15%) | 52 (15%) | 32 (14%) | $\chi^2$=0.03 | 0.9 | 0.900 |
| **Psychiatric illness** | 221 (38%) | 142 (40%) | 79 (35%) | $\chi^2$=1.5 | 0.2 | 0.350 |
| **Chronic disease (any kind)** | 285 (49%) | 170 (48%) | 115 (51%) | $\chi^2$=0.48 | 0.5 | 0.667 |
| **Metabolic disorder** | 243 (42%) | 149 (42%) | 94 (42%) | $\chi^2$=0.01 | >0.9 | 0.900 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Thyroid disorder** | 206 (36%) | 123 (35%) | 83 (37%) | $\chi^2$=0.25 | 0.6 | 0.700 |
| **Endometriosis** | 59 (10%) | 33 (9.3%) | 26 (12%) | $\chi^2$=0.73 | 0.4 | 0.560 |
| *Socio-economic factors* | | | | | | |
| **Education** | | | | Fisher's ET | 0.2 | 0.350 |
| Primary | 5 (0.9%) | 4 (1.1%) | 1 (0.4%) | | | |
| Secondary | 437 (76%) | 258 (73%) | 179 (80%) | | | |
| Tertiary | 136 (24%) | 91 (26%) | 45 (20%) | | | |
| **Residence** | | | | $\chi^2$=2.2 | 0.3 | 0.467 |
| Capital | 273 (47%) | 163 (46%) | 110 (49%) | | | |
| City | 72 (12%) | 40 (11%) | 32 (14%) | | | |
| Town, village | 233 (40%) | 150 (42%) | 83 (37%) | | | |

Continuous variables are expressed as mean ± standard deviation (SD) and range, categorical variables are expressed as numbers and percentages. The p-values are calculated by Wilcoxon rank sum test, Pearson's Chi-squared test or Fisher's exact test. The q values represent false discovery rate correction (adjusted p value) for multiple testing. The bold values in the table represent significant findings. BMI: body mass index; Fisher's ET: Fisher's exact test.

4.2.2. Regression analysis

Logistic regression showed that cyclothymic, depressive, and anxious temperaments were associated with infertility treatment success in the regression models corrected for age, BMI, socioeconomic, and clinical history parameters. Cyclothymic (odds ratio (OR) = 0.91 CI: 0.86–0.96, $p = 0.001$), depressive (OR = 0.91 CI: 0.86–0.97, $p = 0.006$), and anxious (OR = 0.94 CI: 0.9–0.97, $p = 0.001$) affective temperaments significantly decreased the odds of clinical pregnancy. Apart from affective temperaments, only age, BMI, and previous miscarriage were shown to be predictors of infertility treatment success. Table 5 presents the results of the logistic regression analyses.

**Table 5.** Results of logistic regression analyses of possible predictors of assisted reproduction treatment success (clinical pregnancy) (69).

| | Model 1 | | | Model 2 | | | Model 3 | | | Model 4 | | | Model 5 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Predictors** | **OR** | **95% CI** | **p** | **OR** | **95% CI** | **p** | **OR** | **95% CI** | **p** | **OR** | **95% CI** | **p** | **OR** | **95% CI** | **p** |
| **Age** | **0.87** | **0.83-0.91** | **<0.001** | **0.87** | **0.84-0.91** | **<0.001** | **0.87** | **0.83-0.91** | **<0.001** | **0.88** | **0.84-0.91** | **<0.001** | **0.88** | **0.84-0.92** | **<0.001** |
| **BMI** | 0.96 | 0.92-1 | 0.059 | **0.95** | **0.91-0.99** | **0.019** | **0.96** | **0.92-1** | **0.032** | **0.96** | **0.92-0.99** | **0.030** | **0.95** | **0.91-0.99** | **0.019** |
| **Cyclothymic** | **0.91** | **0.86-0.96** | **0.001** | | | | | | | | | | | | |
| **Depressive** | | | | **0.91** | **0.86-0.97** | **0.006** | | | | | | | | | |
| **Anxious** | | | | | | | **0.94** | **0.9-0.97** | **0.001** | | | | | | |
| **Irritable** | | | | | | | | | | 0.99 | 0.94-1.05 | 0.825 | | | |
| **Hyperthymic** | | | | | | | | | | | | | 1.03 | 0.99-1.08 | 0.157 |
| **Infertile for (>2 years)** | 0.96 | 0.66-1.4 | 0.843 | 0.97 | 0.67-1.41 | 0.888 | 0.96 | 0.66-1.39 | 0.822 | 0.92 | 0.64-1.34 | 0.675 | 0.93 | 0.64-1.34 | 0.699 |
| **Previous pregnancy** | 0.89 | 0.47-1.67 | 0.709 | 0.90 | 0.48-1.68 | 0.733 | 0.91 | 0.48-1.72 | 0.779 | 0.97 | 0.52-1.81 | 0.927 | 0.97 | 0.52-1.81 | 0.924 |
| **Previous miscarriage** | **2.17** | **1.2-3.96** | **0.011** | **1.97** | **1.1-3.54** | **0.023** | **2.06** | **1.15-3.74** | **0.016** | **1.89** | **1.06-3.37** | **0.031** | **1.84** | **1.03-3.28** | **0.038** |
| **Previous live birth** | 1.25 | 0.67-2.3 | 0.484 | 1.21 | 0.66-2.24 | 0.535 | 1.21 | 0.65-2.23 | 0.540 | 1.16 | 0.63-2.13 | 0.620 | 1.17 | 0.64-2.14 | 0.608 |
| **Psychiatric illness** | 0.89 | 0.6-1.32 | 0.558 | 0.85 | 0.58-1.26 | 0.421 | 0.87 | 0.59-1.29 | 0.499 | 0.74 | 0.5-1.09 | 0.131 | 0.77 | 0.52-1.12 | 0.168 |
| **Chronic disease** | 1.32 | 0.89-1.96 | 0.176 | 1.30 | 0.87-1.93 | 0.197 | 1.34 | 0.9-2.01 | 0.148 | 1.23 | 0.83-1.82 | 0.304 | 1.25 | 0.84-1.85 | 0.272 |
| **Metabolic disorder** | 0.99 | 0.67-1.45 | 0.942 | 1.00 | 0.68-1.46 | 0.984 | 0.99 | 0.67-1.46 | 0.968 | 0.96 | 0.65-1.4 | 0.821 | 0.98 | 0.66-1.43 | 0.901 |
| **Thyroid disorder** | 1.09 | 0.74-1.62 | 0.656 | 1.09 | 0.74-1.61 | 0.656 | 1.08 | 0.73-1.6 | 0.692 | 1.10 | 0.75-1.62 | 0.627 | 1.10 | 0.75-1.63 | 0.620 |
| **Endometriosis** | 1.08 | 0.58-1.99 | 0.802 | 1.04 | 0.57-1.91 | 0.892 | 1.05 | 0.57-1.93 | 0.863 | 1.01 | 0.55-1.85 | 0.966 | 1.01 | 0.55-1.84 | 0.973 |
| **Education (primary)** | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| **Education (secondary)** | 4.55 | 0.52-99.8 | 0.216 | 3.55 | 0.42-78.74 | 0.300 | 4.86 | 0.57-109.4 | 0.200 | 4.21 | 0.51-91.42 | 0.234 | 4.07 | 0.51-87.04 | 0.240 |
| **Education (tertiary)** | 5.96 | 0.7-130.4 | 0.143 | 4.87 | 0.58-107.9 | 0.195 | 6.81 | 0.81-153.2 | 0.119 | 5.98 | 0.74-129.3 | 0.138 | 5.71 | 0.72-121.64 | 0.144 |
| **Residence (capital)** | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| **Residence (city)** | 1.30 | 0.74-2.3 | 0.360 | 1.25 | 0.71-2.21 | 0.432 | 1.27 | 0.72-2.22 | 0.411 | 1.20 | 0.68-2.1 | 0.526 | 1.19 | 0.68-2.08 | 0.544 |
| **Residence (town, village)** | 0.85 | 0.57-1.26 | 0.414 | 0.81 | 0.54-1.19 | 0.284 | 0.84 | 0.57-1.25 | 0.395 | 0.79 | 0.54-1.17 | 0.245 | 0.81 | 0.55-1.21 | 0.305 |

The table shows the results of multivariate logistic regression analyses using age, BMI, change in TEMPS-A scores, socio-economic and clinical history parameters as predictor and clinical pregnancy as outcome variables. Affective temperaments were fit into the multiple regression analyses separately. OR odds ratio, CI confidence interval, BMI body mass index. The bold values in the table represent significant findings.

### 4.2.3. ROC analysis

Based on multiple ROC analyses, cyclothymic scores >4 [sensitivity: 55.8%; specificity: 60.8%; AUC (Area Under the Curve): 0.575], depressive scores >9 (sensitivity: 33.4%; specificity: 74.2%; AUC: 0.556), anxious scores >9 (sensitivity: 40.2%; specificity: 73.3%; AUC: 0.564), irritable scores >3 (sensitivity: 60.1%; specificity: 44.9.2%; AUC: 0.510), and hyperthymic scores >8 (sensitivity: 78.7%;

specificity: 30.0%; AUC: 0.547) yielded the highest Youden index and were thus defined as optimal cut-off values. The distribution of TEMPS-A categories defined by these optimal cut-off values in the overall patient population and among patients with successful and unsuccessful infertility treatment are described in Table 6.

**Table 6.** Distribution of TEMPS-A categories in the overall patient population and among patients with successful and unsuccessful infertility treatment (69).

| Characteristics | | Treatment success (clinical pregnancy) | | | | |
|---|---|---|---|---|---|---|
| | Total | (-) | (+) | Test statistic | p-value | q-value |
| **Number** | 578 | 353 (61%) | 225 (39%) | - | - | - |
| *Affective temperaments* | | | | | | |
| **Cyclothymic>4** | 240 (42%) | **166 (47%)** | **74 (33%)** | $\chi^2$=11 | **<0.001** | **0.005** |
| **Depressive>9** | 176 (30%) | 118 (33%) | 58 (26%) | $\chi^2$=3.8 | 0.051 | 0.128 |
| **Anxious>9** | 202 (35%) | **142 (40%)** | **60 (27%)** | $\chi^2$=11 | **<0.001** | **0.005** |
| **Irritable>3** | 263 (46%) | 164 (46%) | 99 (44%) | $\chi^2$=0.34 | 0.6 | 0.700 |
| **Hyperthymic>8** | 374 (65%) | 217 (61%) | 157 (70%) | $\chi^2$=4.1 | 0.042 | 0.118 |

Categorical variables are expressed as numbers and percentages. The p-values are calculated by Pearson's Chi-squared test. The q values represent false discovery rate correction (adjusted p value) for multiple testing.The bold values in the table represent significant findings.

4.2.4. Regression analysis with cut-off values applied

According to further logistic regression analyses, cyclothymic scores >4 (OR = 0.51 CI: 0.35–0.74, $p < 0.001$], depressive scores >9 (OR = 0.59 CI: 0.4–0.87, $p = 0.009$) and anxious scores >9 (OR = 0.45 CI: 0.31–0.66, $p < 0.001$) independently predict infertility treatment success (clinical pregnancy), along with age, BMI, and previous miscarriage. More specifically, a cyclothymic score >4, depressive score >9, and anxious score >9 decrease the odds of clinical pregnancy after infertility treatment by 49%, 41%, and 55%, respectively (Figure 5). Table 7 summarizes the results of the final logistic regression analyses.

**Table 7.** Results of logistic regression analyses applying optimal cut-off values for affective temperaments (69).

| | Model 1 | | | Model 2 | | | Model 3 | | | Model 4 | | | Model 5 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Predictors** | **OR** | **95% CI** | **p** | **OR** | **95% CI** | **p** | **OR** | **95% CI** | **p** | **OR** | **95% CI** | **p** | **OR** | **95% CI** | **p** |
| **Age** | **0.88** | **0.84-0.92** | **<0.001** | **0.88** | **0.84-0.91** | **<0.001** | **0.87** | **0.84-0.91** | **<0.001** | **0.88** | **0.85-0.92** | **<0.001** | **0.89** | **0.85-0.92** | **<0.001** |
| **BMI** | **0.96** | **0.92-1** | **0.036** | **0.95** | **0.92-0.99** | **0.012** | **0.95** | **0.92-0.99** | **0.013** | **0.95** | **0.92-0.99** | **0.012** | **0.95** | **0.91-0.98** | **0.007** |
| **Previous miscarriage** | **1.88** | **1.27-2.79** | **0.002** | **1.77** | **1.2-2.61** | **0.004** | **1.87** | **1.26-2.77** | **0.002** | **1.77** | **1.2-2.61** | **0.004** | **1.70** | **1.16-2.51** | **0.007** |
| **Cyclothymic** | **0.51** | **0.35-0.74** | **<0.001** | | | | | | | | | | | | |
| **Depressive** | | | | **0.59** | **0.4-0.87** | **0.009** | | | | | | | | | |
| **Anxious** | | | | | | | **0.45** | **0.31-0.66** | **<0.001** | | | | | | |
| **Irritable** | | | | | | | | | | 0.84 | 0.59-1.2 | 0.336 | | | |
| **Hyperthymic** | | | | | | | | | | | | | 1.44 | 1-2.1 | 0.054 |

The table shows the results of multivariate logistic regression analyses using age, BMI, previous miscarriage, and TEMPS-A scores with optimal cut-off values applied as predictor and clinical pregnancy as an outcome variables. Affective temperaments were fit into the multiple regression analyses separately. OR odds ratio, CI confidence interval, BMI body mass index. The bold values in the table represent significant findings.

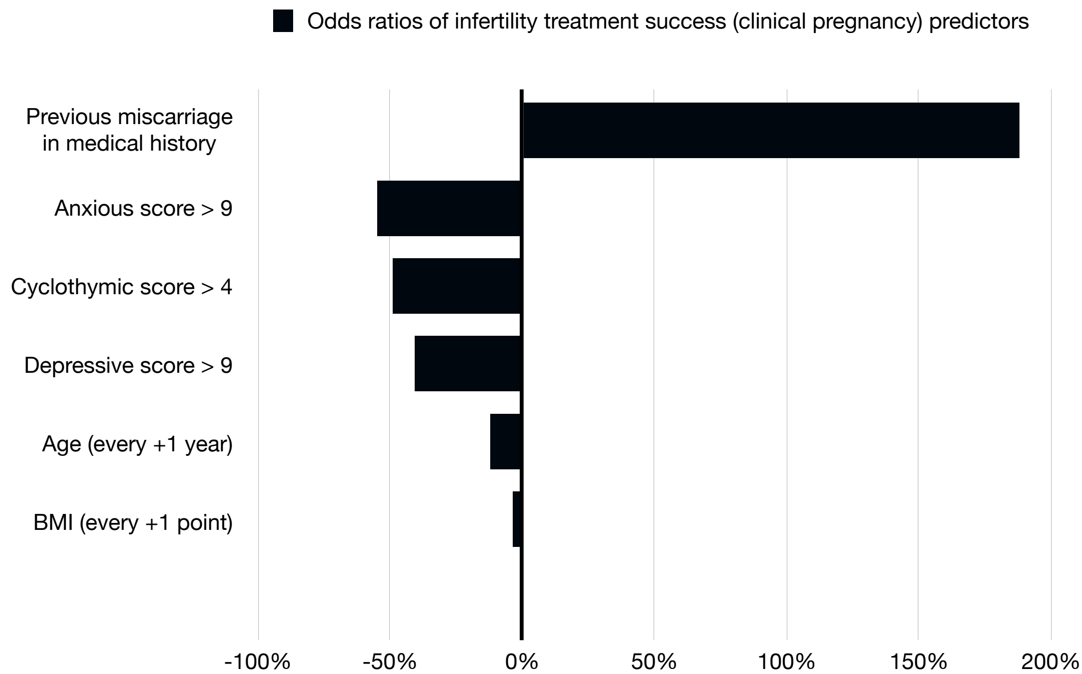


**Figure 5.** Statistically significant predictors of infertility treatment success (69).

## 4.3. Study 3: Adherence as a mediator of affective temperaments on infertility treatment outcomes

### 4.3.1. Descriptive statistics

The analysis included 308 women (22–46 years of age) who underwent infertility treatment within the last three years and whose treatment plan included both diet and regular physical activity. Since this study is a continuation of the previous study (69), as a first step, the main characteristics of this subgroup of 308 patients were compared with the entire population of 578 patients. No statistically significant difference was found between the demographic, anthropometric, psychometric, and medical characteristics of the two groups except for BMI (25.83 ± 5.87 vs. 24.24 ± 4.90 $kg/m^2$ (W=103380, $p < 0.001$)) and diagnosed metabolic disorder (79% vs. 42% ($\chi^2$=108, $p<0.001$)) which is a natural consequence of the fact that this group includes the patients who needed to diet and exercise.

In this current subgroup, 201 (65%) of the participants were primarily infertile, 45 (15%) already had at least one child from a previous pregnancy, while 62 (20%) did not have children yet but already achieved pregnancy which ended in miscarriage(s). The mean age of our cohort was 35.51 ± 4.78 years, and the mean BMI was 25.83 ± 5.87 $kg/m^2$. The probable co-factors associated with infertility were highly variable among the patients, the most typical of which included various problems of metabolic disorders (79%), thyroid disorders (44%), endometriosis (9.1%), or the combination of these. The applied assisted reproduction treatments were diverse. In most cases, ovarian stimulation was applied according to one of the standard protocols (63), followed by either traditional in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI), supplemented as necessary with medications or other kinds of treatment for the presumed problems behind the infertility. All of the patients had to follow a specific diet and physical activity schedule as part of their treatment, but only 43% of the patients adhered to the diet, and 38% adhered to the physical activity recommended by their doctor. The applied infertility treatment resulted in clinical pregnancy in 116 out of 308 cases (38%).

The mean age of patients who successfully became pregnant after the treatment was approximately two years less than those who failed to conceive after treatment

(34.36 ± 4.61 vs 36.20 ± 4.76 years (W=13592, $p = 0.001$)). No statistically significant difference could be observed regarding BMI and previous miscarriage. Regarding affective temperaments, the mean score of cyclothymic and anxious temperaments proved to be significantly lower in the pregnant cohort compared to the non-pregnant one (4.22 ± 4.15 vs 5.21 ± 4.16 points (W=12985, $p = 0.014$) and 6.80 ± 5.20 vs 8.20 ± 5.54 points (W=12782, $p = 0.03$), respectively). The proportion of those patients who adhered to the diet plan was significantly higher in the group that successfully became pregnant (55% vs 35% ($\chi^2$=12, p<0.001)). The adherence rate to physical activity did not differ significantly in the two groups. Demographic parameters, adherence, and scores in the different scales of affective temperaments are summarized in Table 8.

**Table 8.** TEMPS-A scores, adherence, and previously identified infertility risk factors as covariates in successful and unsuccessful infertility treatment patients (70).

| **Characteristics** | | **Treatment success (clinical pregnancy)** | | | |
|---|---|---|---|---|---|
| | **Total** | **(-)*** | **(+)*** | **Test statistic** | **p-value** |
| **Number** | 308 | 192 (62%) | 116 (38%) | - | - |
| *Covariates* | | | | | |
| **Age (years)** | 35.51 (4.78) [22.00, 46.00] | **36.20 (4.76) [22.00, 45.00]** | **34.36 (4.61) [24.00, 46.00]** | W=13,592 | **0.001** |
| **BMI (kg/m2)** | 25.83 (5.87) [16.50, 55.60] | 26.36 (6.26) [16.50, 55.60] | 24.95 (5.07) [17.40, 42.40] | W=12,430 | 0.088 |
| **Previous miscarriage** | 102 (33%) | 56 (29%) | 46 (40%) | $\chi^2$=3.6 | 0.058 |
| *Affective temperaments* | | | | | |
| **Cyclothymic** | 4.84 (4.18) [0.00, 19.00] | **5.21 (4.16) [0.00, 18.00]** | **4.22 (4.15) [0.00, 19.00]** | W=12,985 | **0.014** |
| **Depressive** | 7.43 (2.95) [0.00, 17.00] | 7.69 (2.95) [2.00, 17.00] | 7.00 (2.93) [0.00, 15.00] | W=12,523 | 0.066 |
| **Anxious** | 7.68 (5.45) [0.00, 22.00] | **8.20 (5.54) [0.00, 22.00]** | **6.80 (5.20) [0.00, 22.00]** | W=12,782 | **0.03** |
| **Irritable** | 4.12 (3.54) [0.00, 16.00] | 4.27 (3.66) [0.00, 16.00] | 3.87 (3.34) [0.00, 15.00] | W=11,767 | 0.4 |
| **Hyperthymic** | 10.06 (4.09) [0.00, 20.00] | 9.76 (4.06) [1.00, 20.00] | 10.57 (4.12) [0.00, 20.00] | W=9,699 | 0.057 |
| *Adherence* | | | | | |
| **Adhered to diet** | 131 (43%) | **67 (35%)** | **64 (55%)** | $\chi^2$=12 | **<0.001** |
| **Adhered to physical activity** | 117 (38%) | 70 (36%) | 47 (41%) | $\chi^2$=0.51 | 0.5 |

Continuous variables are expressed as mean ± standard deviation (SD) and range, categorical variables are expressed as numbers and percentages. The p-values are calculated by Wilcoxon rank sum test and Pearson's Chi-squared test. The bold values in the table represent significant findings. BMI: body mass index.

### 4.3.2. Regression analyses

Based on univariate regression analysis, adherence to physical activity didn't (OR=1.229 (p=0.413)), but diet adherence increased the odds of infertility treatment success by 130% (OR=2.299 (p=0.001)), and thereby, possibly could be a potential mediator between affective temperaments and infertility treatment success. Table 9 presents the results of the univariate logistic regression analyses of diet and sport adherence on assisted reproduction treatment success (clinical pregnancy), adjusted for age, BMI, and previous miscarriage as covariates.

**Table 9.** Results of univariate logistic regression analyses of diet and sport adherence on assisted reproduction treatment success (clinical pregnancy) (70).

| Variable | OR | 95% CI | | p |
|---|---|---|---|---|
| **Diet adherence** | **2.299** | **1.408** | **3.755** | **0.001** |
| **Sport adherence** | 1.229 | 0.750 | 2.012 | 0.413 |

The table shows the results of univariate logistic regression analyses using diet and sport adherence as exposure variables, and infertility treatment success (clinical pregnancy) as outcome variable. Models are adjusted for age, BMI, and previous miscarriage. OR: odds ratio CI:confidence interval. The bold values in the table represent significant findings.

### 4.3.3. Causal mediation analyses

Based on causal mediation analysis, higher depressive and anxious temperament scores were directly associated with a lower likelihood of achieving clinical pregnancy (direct effect: OR=0.369 (p=0.023), and OR=0.554 (p=0.013), respectively), with effects not mediated by diet adherence (mediation effect: OR=0.917 (p=0.259), and OR=0.954 (p=0.284), respectively) (Figure 6B and C); higher irritable affective temperament scores indirectly decreased the likelihood of achieving clinical pregnancy, mediated by diet adherence (mediation effect: OR=0.885 (p=0.027), direct effect: OR=0.692 (p=0.307)) (Figure 6D); while higher cyclothymic affective temperament scores decreased the likelihood of achieving clinical pregnancy both directly (OR=0.492 (p=0.027)) and indirectly, mediated by diet adherence (OR=0.891 (p=0.034)) (Figure 6A). Hyperthymic affective temperament had no statistically significant effect on infertility treatment success. Table 10 presents the results of the causal mediation analyses.

**Table 10.** Results of causal mediation analysis of affective temperaments on clinical pregnancy outcome with diet adherence as mediator (70).

| | Mediation effect | | | | Direct effect | | | | Total effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure | OR | 95% CI | | p | OR | 95% CI | | p | OR | 95% CI | | p |
| Cyclothymic | **0.891** | **0.801** | **0.991** | **0.034** | **0.492** | **0.262** | **0.921** | **0.027** | **0.438** | **0.234** | **0.821** | **0.010** |
| Depressive | 0.917 | 0.788 | 1.066 | 0.259 | **0.369** | **0.157** | **0.870** | **0.023** | **0.338** | **0.142** | **0.807** | **0.015** |
| Anxious | 0.954 | 0.876 | 1.040 | 0.284 | **0.554** | **0.348** | **0.884** | **0.013** | **0.529** | **0.330** | **0.849** | **0.008** |
| Irritable | **0.885** | **0.795** | **0.986** | **0.027** | 0.692 | 0.341 | 1.404 | 0.307 | 0.612 | 0.300 | 1.251 | 0.178 |
| Hyperthymic | 0.992 | 0.886 | 1.111 | 0.893 | 1.764 | 0.980 | 3.173 | 0.058 | 1.750 | 0.962 | 3.184 | 0.067 |

The table shows the results of mediation analysis using 10 points of change in TEMPS-A scores, diet adherence and clinical pregnancy as exposure, mediator and outcome variables, respectively. Population: patients whose treatment plan includes both diet and sport recommendation (n=308). The models are adjusted for age, BMI, and previous miscarriage. CI confidence interval, OR odds ratio. The bold values in the table represent significant findings.

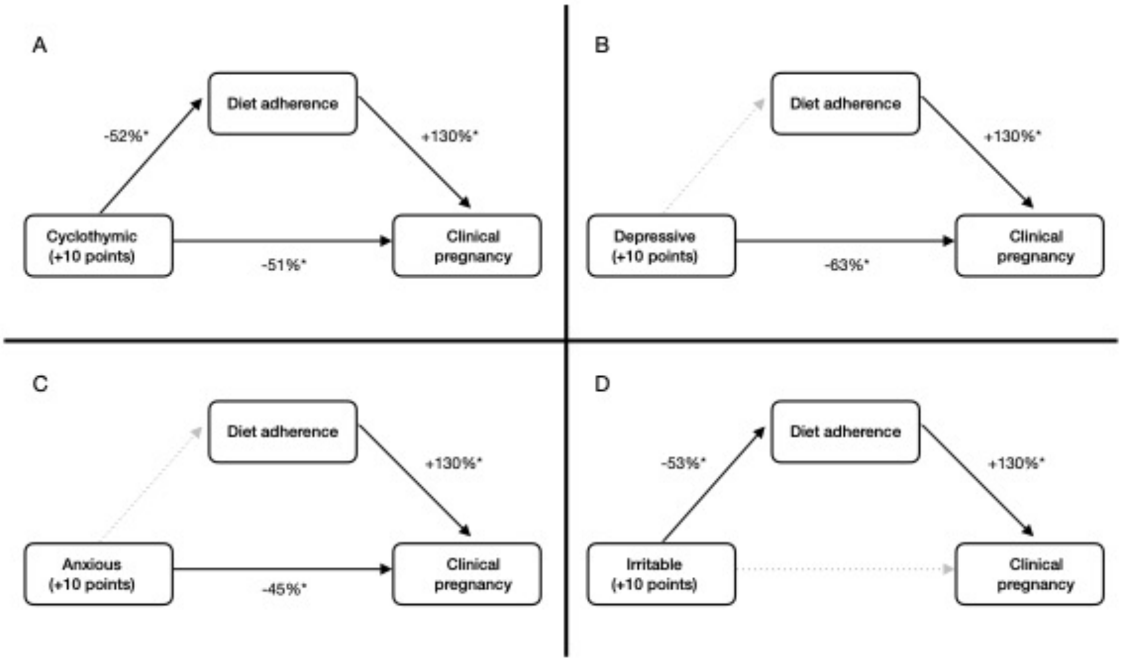


**Figure 6. Mediation analyses results.** A: Direct and indirect effects of cyclothymic affective temperament on infertility treatment success, the latter mediated by diet adherence. B and C: Direct effect of depressive and anxious affective temperaments on infertility treatment success, not mediated by diet adherence. D: Indirect effect of irritable affective temperament on infertility treatment success, mediated by diet adherence. Solid arrows and starred effect sizes indicate significant effects, while dotted arrows indicate nonsignificant pathways (70).

# 5. DISCUSSION

Our studies aimed to investigate 1) the effect of affective temperaments on treatment adherence using a systematic review and meta-analytic approach, followed by a retrospective cohort study evaluating 2) the influence of affective temperaments on fertility treatment, and thereafter a mediation analysis to evaluate 3) whether adherence to physician-prescribed diet and physical activity recommendations mediates the effect of affective temperaments on infertility treatment outcomes among women attempting assisted reproduction.

## 5.1. Study 1: Affective temperaments on adherence

A comprehensive meta-analysis of nine studies, incorporating a total of 1138 subjects in total, revealed strong and adverse correlations between affective temperament scores and adherence in the case of cyclothymic, irritable, and depressive temperaments, both in psychiatric and non-psychiatric populations. These findings suggest that specific temperament traits contribute to decreased adherence to treatment. As a consequence, developing screening tools, risk indicators, and targeted psychotherapeutic, educational, and supportive strategies may enhance adherence by recognizing temperament-related barriers to non-adherence. Gaining insight into how these temperament traits influence attitudes, beliefs, emotions, and behaviors related to medication adherence could provide a novel and crucial possibility to develop personalized patient education, support systems, and intervention methods aimed at mitigating adherence challenges and fostering active patient participation in their treatment plans.

Among the five affective temperaments, cyclothymic, irritable, and depressive temperaments stood out as significant contributors to an increased likelihood of non-adherence to prescribed therapies. Examining the characteristics of these temperament types may provide valuable insights into their influence on adherence behaviors and potential intervention strategies. Generally, individuals with cyclothymic and irritable temperaments exhibit less adaptive responses to distressing events (36). Consistent with Kraepelin's early conceptualizations, cyclothymic and irritable temperaments are characterized by a predisposition toward heightened emotional reactivity and an intolerance of subjective pain, particularly in response to intense stressful or painful experiences (24, 35). Additionally, these temperaments are also linked to feelings of hopelessness (71). Consequently, individuals with these temperaments may struggle with the commitment required for long-term medication adherence, find it challenging to accept chronic illness as an unchangeable reality, and experience difficulties in tolerating the side effects of their prescribed medications.

It is essential to acknowledge that adherence in clinical practice is a multifaceted construct influenced by numerous factors. While emerging research supports the role of temperament in adherence across psychiatric and non-psychiatric populations, various other determinants, including disease-specific variables and illness stages, also play a role. For example, in psychiatric care, adherence to antipsychotic medication is strongly associated with a lack of insight into one's condition (72). Conversely, non-adherence in depression is often linked to cognitive factors rather than a lack of motivation to recover from acute depressive episodes (41). Additionally, fear of stigma can contribute to non-adherence among individuals prescribed psychotropic medications (41), whereas this concern is generally absent in chronic somatic illnesses (73). In diabetes treatment, non-adherence to insulin is more prevalent than non-adherence to oral antidiabetic medications, often due to fear of injections or the embarrassment of administering insulin in public (74). These examples highlight how different patient populations encounter unique barriers to adherence. Although current data limitations don't allow such subtler distinction, the performed subgroup analysis suggests that the effects of cyclothymic, irritable, and depressive temperaments on adherence do not significantly differ between psychiatric and non-psychiatric groups. One possible explanation is that these temperament traits exert a direct influence on adherence, irrespective of the patient population. Alternatively, they may play an indirect moderating role by interacting with different underlying adherence-related factors, finally all resulting in non-adherence. For instance, among psychiatric patients, cyclothymic temperament has been linked to negative attitudes toward psychotropic medications and their side effects, which may lead to decreased adherence (38). In contrast, among individuals with diabetes, cyclothymic temperament has been associated with unhealthy eating behaviors, which could indirectly impact adherence to medical recommendations and overall disease management (31). While both direct and indirect influences of temperament on adherence presumably exist, further research is needed to clarify the causal mechanisms involved.

Moreover, multiple moderators and mediators may interact with temperament traits, contributing to the variability observed in adherence-related behaviors. Several patient-specific risk and protective factors for adherence have been identified so far—some of which may also be influenced by affective temperaments. These include, but are not limited to, socio-economic status, cultural norms, social pressures, stigma, adolescence, advanced age, loneliness, psychiatric disorders associated with the disease, personality disorders, comorbid medical conditions, substance use, cognitive impairments, pregnancy, disease severity, poor insight, and negative perceptions of medication (41).

In summary, adherence is a complex construct shaped by numerous moderating and mediating factors. Future research should prioritize identifying these external variables that indirectly influence temperament-related expressions or modulate their impact on treatment adherence. Understanding the different causal pathways linking temperament to adherence in various illnesses is particularly crucial. Given that affective temperaments are genetically and biologically determined, remain stable over time, and are not easily modified through psychological or psychotherapeutic interventions, directly altering them is not a realistic goal—even within the framework of personalized patient care. However, while temperament may influence adherence through inherent behavioral tendencies (e.g., individuals with cyclothymic temperament being less tolerant of subjective pain), its effect is often mediated by how individuals perceive and process external stimuli (75, 76). These mediating factors, in contrast to temperament itself, can be modified using psychological and therapeutic techniques.

Therefore, rather than focusing psychotherapy efforts on modifying affective temperaments themselves, research should first identify the key mediating and moderating factors, followed by targeting them through educational, supportive, and psychotherapeutic interventions to enhance treatment adherence and improve overall treatment outcomes.

## 5.2. Study 2: Affective temperaments on infertility treatment outcomes

Based on our retrospective cohort study of 578 patients undergoing infertility treatment, our results indicated that beyond conventional risk factors, cyclothymic, depressive, and anxious affective temperaments serve as independent predictors of infertility treatment success. Patients with elevated scores in these temperament categories exhibited lower odds of achieving clinical pregnancy following infertility treatment. Additionally, besides known predictors of infertility treatment success, such as age, BMI, and history of miscarriage (77-79), other somatic and socio-economic variables appeared to have minimal or negligible influence on treatment outcomes.

The impact of personality traits and psychological factors on various medical conditions is becoming increasingly recognized—not only in disease onset but also in long-term prognosis and therapeutic efficacy. Affective temperaments may contribute to these outcomes through both direct and indirect pathways involving multiple mechanisms (16, 18, 21, 80-86). In the context of infertility, these temperaments are not only closely associated with the related heightened levels of anxiety and depression but also with increased emotional sensitivity and reactivity to stress. Individuals exhibiting these traits are more susceptible to developing depressive symptoms when faced with infertility-related stressors (3). This relationship suggests that affective temperaments could play a role in amplifying emotional distress, thereby influencing treatment outcomes (7). Despite these insights, only a limited number of studies have explored the connection between temperament and infertility. A few research have examined the role of personality traits in predicting IVF success, with findings indicating that neuroticism may negatively impact in vitro fertilization success rates (87, 88) and intensify adverse emotional responses to unsuccessful treatment attempts (89). Also, previous studies have shown that mental health conditions such as anxiety and depression can significantly hinder infertility treatment outcomes (48, 90, 91).

Our findings suggest that among women facing infertility challenges, temperament profiles have a substantial impact on their likelihood of getting pregnant, highlighting important clinical implications for fertility treatments. While affective temperaments remain relatively stable over an individual's lifetime, they interact with modifiable risk factors of infertility, including depression, anxiety (7), lifestyle habits (such as weight, nutrition, and exercise), smoking, and other self-harm behaviors (80, 92). Additionally, they influence adherence to treatment regimens, medication protocols, and lifestyle modifications prescribed by healthcare providers (29). Future research should aim to elucidate the specific psychological and behavioral mechanisms mediating the link between temperament and infertility treatment outcomes. Understanding these pathways—whether through cognitive patterns, emotional stability, or behavioral tendencies—could lead to more precise, patient-centered interventions. By incorporating temperament-based screening strategies, fertility specialists can identify high-risk patient groups early in the treatment process. This approach enables targeted interventions to address the negative consequences associated with certain temperament profiles. Potential strategies may include managing depression and anxiety through psychotherapy or pharmacological treatment, reinforcing adherence with structured guidance and education, and providing tailored support for lifestyle changes. While further studies are needed to refine our understanding of the intricate relationships between affective temperaments, coping mechanisms, and lifestyle influences on infertility treatment success, our results already offer a valuable tool for clinical psychologists in assisted reproduction centers. Through screening, psychologists can assess which patients may face higher risks of less favorable outcomes and provide them with enhanced support across various temperament-related behaviors, emotional coping strategies, and lifestyle factors—ultimately improving their chances of a successful fertility treatment outcome.

## 5.3. Study 3: Adherence as a mediator of affective temperaments on infertility treatment outcomes

Our retrospective cohort study of 308 infertile patients demonstrated that affective temperaments significantly influence the likelihood of achieving pregnancy through fertility treatments, which effect is mediated by adherence to dietary recommendations but not by adherence to physical activity guidelines as part of the treatment plan. While hyperthymic temperament had no measurable effect, the other four affective temperament types were associated with a reduced chance of treatment success, with irritable and cyclothymic temperaments exerting their influence entirely or partially through their impact on dietary adherence.

We have already seen that affective temperaments influence the success of infertility treatments; however, as affective temperaments are not modifiable themselves, it is essential to identify and address the specific psychological or behavioral mechanisms mediating their effects. These could include factors such as adherence to treatment regimens, psychological resilience, or other behavioral tendencies. Understanding these pathways could facilitate psychological screening to personalize treatment approaches and provide targeted psychological support to optimize treatment adherence and, consequently, improve outcomes. This study specifically investigated adherence—both to dietary and exercise recommendations—as a potential mediator of treatment success. While both factors are commonly emphasized in infertility treatment, our results indicated that only dietary adherence mediates the impact of certain affective temperaments on treatment success. Notably, depressive and anxious temperaments were not mediated by dietary adherence, whereas cyclothymic temperament was partially mediated, and in the case of irritable temperament, adherence to diet fully explained its influence on treatment outcomes.

We can only hypothesize about the exact temperament-adherence-outcome mediating mechanism, but overall, it is likely that depressed and anxious individuals may experience lower pregnancy rates due to physiological factors rather than behavioral non-adherence, as they tend to strictly follow medical recommendations. In contrast, individuals with cyclothymic and irritable temperaments may struggle with commitment and persistence, particularly in the face of challenges, making it more difficult to adhere to long-term treatment plans, including dietary recommendations. These difficulties align with prior research indicating that these temperament types are also associated with lower medication adherence (29), heightened sensitivity to distressing experiences (36), and a greater tendency toward emotional instability (24, 35). Consequently, individuals with these temperaments may find it more challenging to sustain the lifestyle modifications necessary for successful infertility treatment.

Our findings have significant implications for clinical practice. Psychological interventions tailored to patients undergoing assisted reproductive treatments can be multifaceted, and meta-analytic data indicates that, in general, integrating psychosocial support with assisted reproduction improves both mental health and pregnancy outcomes (93-99). Beyond routine psychological support, which could prevent the development of emotional adjustment disorders as a consequence of stress and psychological burden associated with infertility and infertility treatment, targeted interventions could also be implemented for patients whose temperament profiles suggest a risk of poor adherence to dietary guidelines. Although affective temperaments cannot be modified through psychotherapy, they can be used as screening tools to identify high-risk individuals, allowing for additional counseling, education, and behavioral interventions to address adherence-related challenges.

Specific strategies, such as structured adherence-improvement protocols like the I.M.P.R.O.V.E. approach, which has been used successfully in PCOS patients (100), could be adapted to address the needs of patients struggling with dietary adherence. Early identification and intervention for high-risk patients would not only improve adherence but also increase overall treatment success, making assisted reproduction more efficient and cost-effective. Moreover, by further investigating the psychological factors mediating temperament-related adherence issues, future research could guide the development of alternative interventions that better support patients who may not respond well to traditional recommendations. In doing so, fertility treatments could become more patient-centered and tailored to individual psychological and behavioral profiles, ultimately enhancing success rates and improving patient well-being.

# 6. CONCLUSIONS

Our studies aimed to investigate the impact of psychological factors on infertility treatment success. Our specific objectives were:

1) To investigate the effect of affective temperaments on treatment adherence using a systematic review and meta-analytic approach.

   Our findings indicate that specific affective temperament traits are associated with an increased likelihood of treatment non-adherence, which in turn can negatively influence treatment outcomes. Although future research is needed—particularly primary studies that systematically examine various clinical and psychosocial moderators across different patient populations—these results highlight the potential clinical value of the TEMPS-A scale. Specifically, it may serve as a useful screening tool prior to treatment to identify individuals at greater risk for non-adherence, enabling the provision of targeted support to enhance adherence. To our knowledge, this is the first meta-analysis to demonstrate that affective temperament scores assessed through the TEMPS-A instrument may help predict the risk of medication non-adherence.

2) To investigate the impact of affective temperaments on infertility treatment outcomes among women attempting assisted reproduction.

   Our findings indicate that affective temperament traits play a significant role in shaping the outcomes of infertility treatments, underscoring important clinical implications. While further research is needed to clarify the mechanisms through which these temperaments exert their influence—particularly to uncover modifiable mediators that could enhance the practical value of these insights beyond risk screening—the current results suggest that assessing affective temperaments could be a valuable tool for professionals working in ART centers to identify individuals at greater risk for unfavorable outcomes, supporting a more personalized, targeted care approach and improving the overall cost-effectiveness of interventions. To our knowledge, this study is the first to examine the link between affective temperaments and the success of infertility treatment.

3) To evaluate whether adherence to physician-prescribed diet and physical activity recommendations mediates the effect of affective temperaments on infertility treatment outcomes.

Our findings indicate that specific affective temperament traits are predictive of dietary adherence, and that greater adherence to prescribed dietary guidelines may enhance the likelihood of successful infertility treatment outcomes. Given that dietary non-adherence is a modifiable risk factor of treatment success, evaluating affective temperaments prior to initiating treatment may help identify patients at higher risk for non-adherence. This, in turn, could allow for the implementation of individualized psychological support or interventions aimed at improving adherence, potentially increasing the chances of pregnancy and live birth among women undergoing IVF. To the best of our knowledge, this is the first study to explore the possible mediating role of lifestyle adherence in the connection between affective temperaments and infertility treatment outcomes.

# 7. SUMMARY

Infertility has a multifactorial background, where both physiological and psychological factors play a role in development and outcome. While affective temperaments have been linked to the onset, progression, and treatment outcomes of various medical conditions, their specific relationship with infertility and its treatment has remained unexplored. Also, identifying possible mediating factors through which they exert their influence is still lacking. Emerging evidence, however, suggests that adherence to recommended treatments may be such a mediator. Our studies aimed to investigate 1) the effect of affective temperaments on treatment adherence using a systematic review and meta-analysis approach, followed by a retrospective cohort study evaluating 2) the influence of affective temperaments on fertility treatment, and thereafter a mediation analysis to evaluate 3) whether adherence to physician-prescribed diet and physical activity recommendations mediates the effect of affective temperaments on infertility treatment outcomes among women attempting assisted reproduction. Our results showed that 1) certain affective temperaments predict treatment non-adherence and, thus, impact overall treatment outcomes both in psychiatric and non-psychiatric populations; 2) affective temperaments play a substantial role in determining the success of infertility treatments; and 3) certain affective temperaments are associated with lower adherence to dietary recommendations, which in turn appears to decrease the likelihood of achieving a successful fertility outcome. In clinical practice, the TEMPS-A questionnaire may serve as a valuable screening tool to identify individuals at elevated risk for non-adherence and support them in increasing their adherence in both psychiatric and non-psychiatric populations. In the case of assisted reproduction, screening for affective temperaments could enable healthcare providers working in ART centers to identify high-risk subgroups, thereby facilitating a more personalized and cost-effective approach to care. As adherence to diet is a modifiable risk factor of infertility treatment success, assessing affective temperaments before initiating IVF could help to identify high-risk non-adherent patient groups and offer patient-tailored mental health support or interventions targeting non-adherence, which may help increase the chances of a successful pregnancy and live birth in women undergoing IVF treatment.

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# 9. BIBLIOGRAPHY OF PUBLICATIONS

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- **Szabo, G.**, Fornaro, M., Dome, P., Varbiro, S., & Gonda, X. A bitter pill to swallow? Impact of affective temperaments on treatment adherence: a systematic review and meta-analysis. *Translational Psychiatry*. 2022; *12*(1):360. D1, IF: 6,8
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## Publications not related to the thesis:

- Hargittay, C., Vörös, K., Eőry, A., Márkus, B., **Szabó, G.**, Rihmer, Z., Gonda, X., & Torzsa, P. A cukorbetegség szövődményeinek összefüggése a depressziós és szorongásos tünetekkel. *Orvosi Hetilap*. 2023; *164*(3):79-87.
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