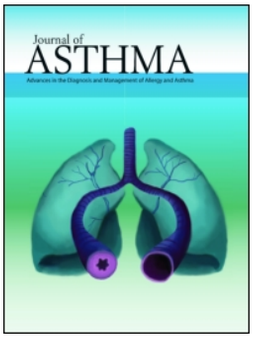

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# Prevalence and predictors of adherence to inhaled corticosteroids in young adults (15-30 years) with asthma: A systematic review and meta-analysis

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**Abstract**

**Objective:** Adherence to inhaled corticosteroids (ICS) is an essential part of asthma management throughout the lifespan, however this may be particularly challenging during the transition into adulthood. This systematic review aimed to determine the prevalence and predictors of adherence to ICS in emerging adulthood.

**Data sources:** MEDLINE, PsycINFO, EMBASE, Scopus and CINAHL were searched with search terms for asthma, ICS, adherence, young adults and predictors combined.

**Study selection:** Studies with participants with diagnosed asthma, currently prescribed ICS, a mean age between 15-30 years and reporting the prevalence and/or assessing predictor(s) of adherence using quantitative methods were included.

**Results:** Twenty-nine studies were identified for inclusion (*K*=29,*N*=187 401). A random effects meta-analysis revealed the pooled prevalence of adherence was 28% (95% CI=20-38%,*k*=16) in studies that provided quantitative information on adherence. Adherence was higher in studies with a mean age <18 years (36%;95% CI=36-37%,*k*= 4). Studies using self-report measures provided higher estimates of adherence (35%;95% CI= 28-42%,*k*=10) than studies using pharmacy refill data (20%;95% CI=9-38%,*k*=6). A narrative review identified personality, illness perceptions and treatment beliefs as potentially important predictors of adherence.

**Conclusion:** Adherence is sub-optimal during emerging adulthood, particularly after age 18. More reliable and objective measures are needed to precisely characterize adherence. Greater research and practice attention to emerging adulthood are needed to guide self-management support in those living with asthma at this important lifespan stage.

**Systematic review registration number:** CRD42018092401

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## Introduction

Asthma is one of the most common non-communicable diseases, with an estimated 358 million people living with the condition worldwide (1). Inhaled corticosteroids (ICS) can effectively control asthma by optimizing lung function, reducing symptoms and disease burden (2). Despite this, up to 60% of individuals with asthma have uncontrolled symptoms (3,4). This leads to increased healthcare use, missed school and workdays, and up to an estimated 383,000 premature deaths each year (5,6). Poor adherence to ICS is a major behavioral contributor to suboptimal asthma control globally (7). Adherence to treatments varies greatly both between and within those living

with asthma, however estimates indicate that overall optimal adherence rates remain relatively low at between 22-63% (7).

Adolescents with asthma typically report poorer adherence than children and adults (8,9). This may be due to the reduction in parental medication management and other self-care tasks that often accompany healthy development in autonomy that occurs through adolescence (10). It has been reported that by age 15, adolescents often take most of the responsibility for taking their daily asthma medication (11). The subsequent stage of psychological development defined as Emerging Adulthood, i.e. 18-29 years, (12) represents a distinct developmental phase between adolescence and adulthood of particular importance in the development of life-long self-management habits. This dynamic period is characterized by exploration of various life directions, increased independence and engagement in health risk behaviors. Concurrently, emerging adults take on responsibility for the self-management of their health. Therefore, this is a critical point to support and understand the self-care challenges of those living with asthma, particularly adherence to ICS, given the unique developmental needs of emerging adults as they transition from pediatric to adult respiratory care (13).

Despite the recognized need to focus on non-adherence to asthma medication in Emerging Adulthood, the prevalence and reasons for non-adherence have not been systematically explored during this developmental stage. The aims of this review are: 1) to provide a prevalence estimate of adherence to ICS in this population, and 2) to synthesize the evidence on predictors of adherence and non-adherence to ICS. Synthesizing evidence on predictors of behavior is highly conducive to informing the development of effective behavior change interventions. However, few reviews have explicitly defined this method of synthesis using an appropriate framework (14). The Theoretical Domains Framework (TDF) integrates the key theories and constructs relevant to behavior change (15). We used this theory-informed approach to understand predictors of adherence and identify potential intervention strategies.

## Methods

This systematic review and meta-analysis are conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (16) and registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD42018092401).

### *Search methods for identification of studies*

MEDLINE, PsycINFO, EMBASE, Scopus and CINAHL electronic databases were searched from database start to June 2018. An updated search was conducted in June 2019. Two independent search strategies were used; one to capture prevalence and one for predictors of adherence. The strategies were informed by relevant reviews in the literature (17,18,19-21). The search strategy was modified for each database, using keywords and MeSH terms where appropriate. Search terms for Asthma were combined with search terms for ICS, adherence, young adults and predictors. An example of the search strategy is shown in Supplementary Appendix 1. Forward and backward reference searching of the included articles were conducted to identify additional relevant articles.

### *Eligibility criteria*

Articles with a sample of participants with diagnosed asthma, currently being prescribed ICS including ICS combination therapies, with a mean age falling between 15-30 years (inclusive) and reporting the prevalence and/or assessing predictor(s) of adherence using quantitative methods

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were included. Intervention studies reporting baseline adherence data were also included. For studies that did not report the mean age of the sample, authors were contacted for this information and decision to include was made on a case-by-case basis. We defined young adults as 15-30 years old for the following reasons: 1) to capture the age at which individuals typically take responsibility for their adherence, 2) to include Emerging Adulthood, 3) to facilitate varying definitions of young adults across the healthcare transition literature (22,23) and 4) there is precedent for focusing on 15-30 years in the context of chronic illness self-management (18). Reviews, discussion papers, conference abstracts or theses, articles published in a language other than English or not available in full text were excluded. A recent review found that excluding grey literature impacts only a minority of medical reviews and meta-analyses (24). Therefore, a pragmatic decision was made to exclude grey literature based on the resources available for this review, i.e. a single PhD scholarship.

***Study selection***

The search results were exported to an EndNote database, where one reviewer (JM) identified and removed duplicates. One reviewer (JM) transferred all unique articles to Covidence database and screened title and abstracts for inclusion. A second reviewer (LVR) independently screened 20% of titles and abstracts. Cohen's kappa was conducted to determine the agreement between the two independent reviewers. Based on guidelines from the literature (25), there was substantial agreement between reviewers, $\kappa$=.652. One reviewer (JM) screened all full texts and a second independent reviewer (LVR) screened 20% of full texts for inclusion. There was a moderate strength of agreement between reviewers, $\kappa$=.418 (25). Reviewers' disagreements at both screening stages reached consensus through discussion. Reasons for exclusion in the full text screening stage are shown in the PRISMA flow chart (Figure 1). One reviewer (JM) conducted forward and backward reference searching of the included papers.

***Data extraction***

Two independent reviewers (JM, SM) extracted the following information from all included studies:

1. Study setting
2. Design
3. Sample size
4. Sample Age M(SD)/Median
5. Gender: Female N(%)
6. Definition of adherence/non-adherence
7. Measure(s) of adherence
8. N adherent(%)
9. Predictor(s) assessed
10. Measure(s) of predictor(s)
11. Significant predictor(s)

The characteristics of included studies can be seen in Table 1 and 2. Minimal disagreements between reviewers were identified in data extraction and were resolved through discussion.

***Risk of bias assessment***

Risk of bias was evaluated by two independent reviewers (JM, SM) using the criteria outlined by Sanderson et al., (26) for assessing quality and bias in observational studies (Figure 2). Each criterion was classified as having a low, unclear or high risk of bias.

***Data analysis and synthesis***

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Statistical analysis was conducted using R and SPSS software. A random effects model was employed to calculate a pooled prevalence of adherence, as the assumptions of a fixed effects model were violated for this analysis. $I^2$ statistic was used to assess between-study heterogeneity (27). Subgroup analyses examined age, method of measurement and method of recruitment as potential moderators of adherence. Results of the studies that were not deemed appropriate for a meta-analysis due to heterogeneity in outcome measure were synthesized using a narrative synthesis. The first author (JM) used the TDF (15) to code predictors of adherence to the most appropriate domain. The TDF includes 14 domains: Knowledge, Skills, Social/professional role and identity, Beliefs about Capabilities, Optimism, Beliefs about Consequences, Reinforcement, Intentions, Goals, Memory, attention and decision processes, Environmental context and resources, Social influences, Emotion and Behavioral Regulation. To accurately and comprehensively capture the predictors in the included studies, we expanded Optimism to an all-encompassing Personality domain. The results of this analysis were also synthesized narratively.

## Results

### *Results of the search*

The original search identified 1280 unique articles, 485 were reviewed in full text. Of these, 23 studies were identified for inclusion. Five additional articles were identified from backward reference searching of the included studies. These results can be seen in the PRISMA flowchart in Figure 1. The updated search identified 99 unique articles, 39 were assessed in full text, of which one study was identified for inclusion.

### *Study characteristics*

Twenty-nine studies were included; 28 reported adherence and 10 reported predictors of adherence. Key study information is presented in Table 1 and 2.

### *Risk of bias*

A summary of the risk of bias assessment is presented in Figure 2.

### *Patient characteristics*

The pooled participant sample was 187 401; however, one study accounted for over 127 000 (67.77%) of these (28). The number of participants included ranged from 6 (29) to 127 081 (28). The mean age of the pooled sample was 23.30 (5.42) years and ranged from 14.68 (30) to 30.40 (31,32). Twenty-three studies had a female majority sample.

### *Prevalence of adherence*

Study information on adherence measure and outcome for all studies reporting adherence is provided in Table 1 and 2. We conducted a meta-analysis of 16 studies; 12 of the studies reporting adherence did not provide the percentage of the sample defined as adherent and were not included in the meta-analysis. Considerable heterogeneity existed among these studies with respect to design, measurement methods and definitions of adherence. These results are synthesised according to the method employed to measure adherence.

### *Meta-analysis*

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Pooled prevalence of adherence was 28% (95% CI=20-38%, $k$=16 $I^2$=100%, p<.001), with rates ranging from 6.00-58.10% and showing significant heterogeneity. The lowest estimate was measured by pharmacy records (28) and the highest by self-report (33).

***Subgroup analysis***

*Age:* The age of the study samples was dichotomized to <18 and 18-30 years, based on the mean age of the sample. Four studies reported a mean age <18 years (34-37,34,35,36) and had a higher pooled adherence estimate (36%; 95% CI=36-37%, $k$=4, $I^2$=0%, $p$=.13) than studies with a mean age of 18-30 years (25%; 95% CI=16-37%, $k$=12, $I^2$=99%, $p$<.01).The forest plot can be seen in Figure 3.

*Adherence measure*: Three measurement methods of adherence were used. The most frequently used method was self-report (33-35,37,39-43). Five studies used pharmacy record data (44,45,32,28,36). One study used a combination of self-report and pharmacy record data (44). We used the lower, more objective estimate from pharmacy refill data, as the overall study estimate and categorised this study as pharmacy refill data. The highest pooled adherence estimate was found for self-report; 35% (95% CI= 28-42%, $k$=10, $I^2$=95%, $p$<.01) as compared to studies using pharmacy refill data (20%; 95% CI=9-38%, $k$=6, $I^2$=95%, $p$<.01). The forest plot is presented in Figure 4.

*Method of recruitment:* Methods of study recruitment were dichotomised to secondary care and non-secondary care. Four studies recruited through secondary care (33-34, 38). The pooled adherence estimate for these studies was 45% (95% CI=32-59%, $k$ =4, $I^2$=89%, $p$<.01). Of the studies that did not recruit through secondary care, the most commonly used method was a healthcare database (28,44,45,36), followed by an educational institution (39,41,42) and pharmacies (43,44,37). One study recruited through primary care (40) and a population survey (35). The pooled adherence estimate for these studies was 24% (95% CI=16-34%, $k$= 12, $I^2$=89%, $p$<.01). The forest plot is shown in Figure 5.

***Narrative synthesis of prevalence of adherence by method of measurement***

Of the remaining 12 studies reporting adherence, six used pharmacy record data (31, 47-50, 51), four used self-report (29, 30, 54, 55,) and two used electronic monitoring to measure adherence (56,76).

***Pharmacy record data***

D'Souza et al., (48) and Mattke et al., (51) used the MPR to measure adherence to ICS. Delea et al., (49) used ICS refill rate in addition to the MPR. None of these studies provided a definition of adherence. In D'Souza et al., (48), the average MPR was 45.7 and 52.4% for the control and intervention group, respectively. In Mattke et al., (53) the overall median of ICS adherence was 15%. Thirdly, in Delea et al., (49) the mean MPR and refill rate in the ICS and Montelukast group was 37.7 (25.9) and 3.04 (2.48), respectively.

Blais et al., (31) measured adherence using the Proportion of Days Covered (PDC) and Proportion of Prescribed Days Covered (PPDC). The mean PPDC and PDC were 52.6% and 19.1%, respectively. Williams et al., (50) used the Continuous Multiple-Interval Measure of Medication Availability (CMA; 52). Baseline adherence in the intervention and control group was 25.6% (37.3) and 27.7% (38.5), respectively. No definition of adherence was used in these studies. Finally, Balkrishnan et al., (47) measured adherence using Steiner's Med-Total Index for controller pharmacotherapy (53). Adherence was defined as a score of 0.8-1.2 (80-120% prescription adherence rate). The mean

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number of ICS refills in the Montelukast and Salmeterol group at baseline were 6.9 (2.8) and 7.4 (3.4), respectively.

***Self-report***

Rhee et al., (30) used two measures: (1) no. of doses missed in the prior 2 weeks and (2) Medication Adherence Report Scale (MARS; 54). The mean number of missed medication days was 3.16 (4.43) and the mean MARS score was 12.73 (4.09). Axelsson et al., (55) also used the MARS to measure adherence. The mean MARS score was 19.04 (3.89). No definition of adherence was used in these studies.

Koufopoulas et al., (56) employed the Simplified Medication Adherence Questionnaire (SMAQ; 57). Nonadherence was defined as >2 missed doses. The mean baseline SMAQ was 1.45 (0.39). Finally, Erickson et al., (29) used the Asthma Self-Reported Medication Compliance Assessment questionnaire (58). Nonadherence was defined as a section-score ≥1. The mean pre-study inhaled medication score was 2.7.

***Electronic monitoring***

Martin et al. (59) used a medication monitor and if this could not be fitted, the medication counter number was recorded. The median adherence measured by the doser and counter was 0.4 and 1.1, respectively. The combined median of both was 0.7. Finally, Britto et al., (60) used SmartInhaler to measure adherence. At baseline, the average adherence rate was 12.5%. These studies did not provide a definition of adherence.

***Narrative synthesis of predictors of adherence***

***Demographics***

Three papers examined seven demographic as predictors of adherence. Two studies investigated the relationship between race/ethnicity and adherence. African American individuals had significantly lower adherence (45). No significant association between having a caregiver born in the US and adherence was found (59). Wells et al., (45) found that women had significantly lower adherence than men, and that older age was positively associated with adherence. Brandt & Dickinson (39) found that financial need significantly predicted poorer adherence. Finally, no significant associations were found between caregiver acculturation, caregiver education level and having child public insurance and adherence (59).

***Disease Characteristics***

Two papers investigated three disease characteristics as predictors of adherence. Significant positive associations were found between well-controlled asthma (43), asthma severity, other asthma controller medication use and adherence (45).

***TDF Domains***

Across 10 studies, predictors were coded to 7 TDF domains. Personality (6 predictors) was coded most frequently followed by Emotion and Beliefs about Consequences (5 predictors); Beliefs about Capabilities, Memory, Attention & Decision Processes and Behavioural Regulation (2 predictors). Knowledge was coded least frequently (1 predictor).

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***Optimism/Personality***

Six predictors across two studies were coded to Personality. Axelsson et al. (55), found that impulsivity was significantly associated with non-adherence (*r*= -0.187). Antagonism (*r*= -0.368) and Alexithymia (*r*= -0.369) were significantly associated with non-adherence in men only.

Kleiger and Dirks (34) found that panic-fear was significantly related to non-adherence. Participants reporting high panic-fear were more likely to be over/under users than those reporting moderate, or low panic-fear, or participants reporting moderate and low panic-fear combined. Participants reporting low panic-fear were more likely to be under users than those reporting moderate, high panic-fear, or those reporting moderate and high panic-fear combined. No significant associations between Negative Affectivity (*r*=.049), Hedonic Capacity (*r*= -.009) and adherence were found (55).

***Emotion***

Three studies investigated five predictors coded to Emotion. Jessop et al., (41) explored the relationship between emotional representations of asthma and adherence. A significant main effect of level of adherence was found. Low adherers demonstrated significantly greater interference for emotional asthma-related words, than medium adherers.

No significant associations were found between adherence and the remaining predictors coded to Emotion; feeling embarrassed about taking medication, feeling that asthma is unfair (39); caregiver and child depression and stress (58).

***Beliefs about Consequences***

Four studies examined a total of five predictors coded to Beliefs about Consequences. Koster et al., (43) found that having stronger necessity beliefs towards ICS was significantly associated with higher adherence, and that indifferent users were significantly more non-adherent, than accepting users.

Secondly, Axelsson (61) found that having no perceived need significantly accounted for 9.3-12.9% of the variance in non-adherence. Having concerns about the medication also made a participant significantly less likely to adhere (39). No significant associations between outcome expectations and medication adherence or missed doses were found (30).

***Beliefs about Capabilities***

One study assessed two predictors coded to Beliefs about Capabilities (30). Firstly, self-efficacy was significantly associated with adherence (*r*=.426). Higher self-efficacy predicted higher medication adherence. Self-efficacy was not significantly associated with missed doses. Secondly, barrier perceptions were significantly associated with higher adherence. Higher barrier perceptions predicted lower adherence. No significant association between barrier perceptions and missed doses was found.

After adjusting for outcome expectations, barrier perception and demographics, higher self-efficacy significantly predicted less missed doses (*r*= -.621). After adjusting for self-efficacy, outcome expectations and demographics, lower barrier perceptions predicted higher adherence (*r*= -.519).

***Memory, Attention & Decision Processes***

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One study examined two predictors coded to Memory, Attention and Decision Processes. Being risk averse and having a low time preference significantly predicted adherence (39).

***Behavioural Regulation***

Two studies assessed two predictors coded to Behavioural Regulation. Once-daily dosing was significantly associated with 19.3% increase in adherence (45). Insufficient routines significantly accounted for 4.6-6.5% of the variance in non-adherence (61).

***Knowledge***

One study investigated one predictor coded to Knowledge (43). Sufficient knowledge about asthma medication was significantly associated with better adherence.

**Discussion**

The included studies produced highly heterogeneous estimates of adherence, likely due to substantial variation in study design, method of measurement and definition of adherence. Approximately 28% of young adults living with asthma adhere to ICS medication as prescribed according to this review. This prevalence estimate is considerably lower than those estimated in the empirical literature on children and adolescents (62), and adults living with asthma (7,9), highlighting the particular need to address non-adherence in this population.

Sub-group analysis suggested the prevalence of adherence is higher in populations under 18 than in those over 18. This is inconsistent with findings from previous reviews (63,64). However, it should be noted that each study categorized as under 18, had a mean age of 15 years. Although it has been reported that by age 15 adolescents have begun taking their asthma medication independently (11), typically, their lifestyle remains structured with parental involvement, i.e. in second-level education in most contexts, living in a home-structured environment. In contrast, age 18 often coincides with beginning third level education or leaving the family home for many, during which this structure is replaced by a dynamic, unpredictable lifestyle characterized by a change of residence, part-time employment, irregular sleep and higher alcohol consumption. This transition may conflict with beliefs and actions required for positive health behavior such as adhering to daily asthma medication.

Sub-analysis by measurement method revealed that self-report yielded the highest estimates of adherence. Different methods of measurement are subject to different reliability and validity issues and yield significantly variable estimates. However, each method provides unique, important information about patient adherence and a combination of objective and subjective measures may be the most appropriate method to determine adherence.

The definition of adherence also varied substantially across studies, with cut-off values of 50, 75 and 80% observed. Studies using 75% based this threshold on a previous finding that 75% adherence was associated with a significant decrease of exacerbations (65). Studies using 50 and 80% provided no justification and so this selection appears arbitrary. Adherence has been defined as 80% in other chronic diseases such as hypertension (66), however, the therapeutic benefit of 80% adherence in asthma remains unknown. Although previous studies have demonstrated a dose-response relationship between greater adherence to ICS and decreased risk of death from asthma (67), the specific rate of adherence to ICS for optimizing lung capacity remains largely unknown. This inconsistency indicates a lack of consensus among researchers and clinicians on optimum adherence in asthma.

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Our final sub-analysis revealed that populations recruited from secondary care are substantially more adherent than those recruited from primary care. Secondary care patients tend to have more symptoms, and therefore, may be more motivated to take medication in the hope of symptom relief. Whereas patients with little or no symptoms would receive no such immediate benefit. In addition, secondary care consultations tend to be longer in duration with increased opportunity to deliver asthma education, in comparison to primary care settings where often the healthcare provider may not have scope or resources to provide this service.

There were limited data on predictors of adherence in young adults and therefore, these findings should be interpreted with caution and within the context of the individual study. Personality was the TDF domain coded most frequently, with four out of six significant predictors of adherence. Traditionally, it has been assumed that personality is stable. However, recent research has demonstrated that, although relatively stable, personality traits change throughout the lifespan, particularly during early adulthood. It has been proposed that personality provides an optimum balance of being sufficiently stable to impact life domains such as health, while also amenable to intervention to significantly improve welfare (68).

Beliefs about Consequences was one of the second most frequently coded domains. Four out of five predictors coded to Beliefs about Consequences were significantly associated with adherence. This is consistent with previous reviews demonstrating the influence of illness perceptions and treatment beliefs in adherence in asthma among adolescents and adults (19,69,21). Recent research has proposed a novel approach for targeting perceptions and beliefs in asthma (70). The reframing approach describes asthma as the lungs being out of balance and ICS as natural helpers to prevent over-reactions. Initial acceptability indicates potential to change perceptions of asthma, i.e. a chronic rather than episodic condition, and improve adherence.

We encountered some difficulties with using the TDF as a coding framework. Some predictors may fall into more than one domain. For example, 'feeling embarrassed about taking medication' may be coded to Emotion or Social or Professional Role and Identity. This problem has previously been reported when coding adherence interventions with the TDF (71), indicating that further clarification of distinct domains is needed to improve the discriminant validity of the framework. Finally, it is surprising that no predictors were coded to the Social Influences domain. Previous reviews have outlined the key role social factors play in adherence in adolescents with asthma (19), warranting future study of social influences as potential predictors of adherence in young adults.

Additional limitations include the restricted range of high-income countries from which the identified studies were conducted. Many low and middle-income countries also have a high prevalence of the disease and asthma deaths (72,73). In some of these economically underdeveloped contexts the availability of ICS is likely to be the more pressing challenge for managing asthma related morbidity and mortality rather than adherence to treatments. In these geographic contexts ICS availability may also influence the adherence estimates in the included studies. Even in contexts where medication is, in theory, readily available there are disparate funding models that influence the availability of ICS. For example, in the US Medicaid covers the cost of asthma inhalers however, this program is only offered to those with limited income. There is no other state funding available for asthma medication. In contrast, the Dutch government is responsible for the accessibility of the healthcare system in the Netherlands. Health insurance is compulsory for all and covers healthcare and medication costs including asthma inhalers.

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Most of the included studies were observational and it has been argued that such studies are more susceptible to bias. However, there is a lack of validated tools for assessing bias for this study design. Therefore, we used criteria outlined by Sanderson et al. (26), in a review on bias assessment tools for observational studies in epidemiology, which has been used in previous adherence reviews (17). Finally, although such heterogeneity between studies may question the validity of this analysis, a decision not to conduct the meta-analysis would fail to synthesize this data in a meaningful manner (74).

**Conclusion**

To our knowledge, this is the first review to systematically synthesize the range of studies that have estimated the prevalence of and reported predictors of adherence to ICS in young adults living with asthma. The findings indicate that adherence to ICS is a significant problem in this population at this potentially challenging transition in the lifespan. Therefore, a significant proportion are not benefiting from effective asthma treatment in early adulthood, leading to a high prevalence of uncontrolled asthma. This new analysis provides an initial description of the problem and identifies several variables that could provide the focus for future intervention design that aim to improve adherence.

**Declaration of interest**
The authors report no conflicts of interest.

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**Example of search strategies used in Medline**

**Medline > Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present**

**Search 1**

**1.** Asthma/
**2.** (asthma*).ab,ti.
**3.** 1 or 2
**4.** Beclomethasone/
**5.** Anti-Asthmatic Agents/
**6.** Asthma/dt [drug therapy]
**7.** (inhaled corticosteroid*).ab,ti.
**8.** (inhaler* or controller medication* or maintenance therap*).ab,ti.
**9.** 4 or 5 or 6 or 7 or 8
**10.** Medication adherence/
**11.** Patient Compliance/
**12.** (medication adheren*).ab,ti.
**13.** (adheren* or nonadheren* or non-adheren* or non adheren* or complian* or noncomplian* or non-complian* or non complian*).ab,ti.
**14.** 10 or 11 or 12 or 13
**15.** Young adult/
**16.** Adolescent/
**17.** (young adult* or young people* or youth* or adolescen* or teenage* or teen*).ab,ti.
**18.** 15 or 16 or 17
**19.** 3 and 9 and 14 and 18

**Search 2**

**1.** Asthma/
**2.** (asthma*).ab,ti.
**3.** 1 or 2
**4.** Beclomethasone/
**5.** Anti-Asthmatic Agents/
**6.** Asthma/dt [drug therapy]
**7.** (inhaled corticosteroid*).ab,ti.
**8.** (inhaler* or controller medication* or maintenance therap*).ab,ti.
**9.** 4 or 5 or 6 or 7 or 8

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**10.** Medication adherence/
**11.** Patient Compliance/
**12.** (medication adheren*).ab,ti.
**13.** (adheren* or nonadheren* or non-adheren* or non adheren* or complian* or noncomplian* or non-complian* or non complian*).ab,ti.
**14.** 10 or 11 or 12 or 13
**15.** (predictor* or determin* or caus* or influenc* or barrier* or factor* or reason* or facilitat*).ab,ti.
**16.** Young adult/
**17.** Adolescent/
**18.** (young adult* or young people* or youth* or adolescen* or teenage* or teen*).ab,ti.
**19.** 16 or 17 or 18
**20.** 3 and 9 and 14 and 15 and 19

Table 1. Summary of studies reporting adherence to ICS

| Reference | Setting | Design | Sample | Age M(SD) | Gender: Female N(%) | Adherence definition | Adherence measure(s) | N adherent (%)/ Adherence outcome |
|---|---|---|---|---|---|---|---|---|
| Axelsson et al. 2009 | Population database West Gothia, Sweden) | Cross-sectional | 268 | 22(1) | 165(61.6) | Low MARS score indicate low levels of adherence | Medication Adherence Report Scale (MARS) | MARS M(SD) = 19.04 (3.89) |
| Balkrishnan et al., 2005 | Medicaid database, North Carolina, US | Retrospective cohort | 198 | 23 | 111(56.1) | A score of ≥0.8 and <1.2 (80-120% prescription adherence rate) | Modified Steiner's Med-Total Index for controller pharmacotherapy; (days of supply dispensed)/(days between prescription refills-no. of days person was in hospital) | Motelukast group: 6.9 (2.8) refills. Salmeterol group: 7.4 (3.4) refills. |
| Blais et al., 2011 | Healthcare databases Quebec, Canada | Retrospective cohort | 4190 | 30.4(7.3) | 2491(59.4) | | Proportion of Prescribed Days Covered (PPDC); (total days' supply dispensed/total days' supply prescribed); (patient and prescriber nonadherence-patient nonadherence)/ patient and prescriber nonadherence) | Patients had a mean of 7.3 months' supplies prescribed (1.6 new prescriptions with 5.7 refills). Up to 18% received 1 new prescription (i.e, no refills) during follow-up. The mean PPDC and PDC over 12 months were 52.6 and 19.1%, respectively. |
| Boulet et al., 2017 | Outpatient clinics Quebec, Canada | Cross-sectional | 150. Young subjects with asthma, I.e. | 26(5) | 32(64) | 1) Visual Analog Scale (VAS): Low | 1) VAS 2) Modified Morisky scale | (1) VAS (N); Low adherence: |

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| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | group with appropriate age: 50 | | | adherence:<50 % of prescribed doses, moderate adherene:50-80%, high adherence:>80 %. 2) Morisky scale: Low adherence: a score of 3/4, medium adherence:1/2, high adherence:0 | | 2, Moderate adherence: 13, High adherence: 19. Score(%) =80(21). (2) Morisky; Low adherence: 7, moderate adherence: 18, high adherence: 10. Score (No. of yes) M(SD)=1.3(1.2) |
| Brandt & Dickinson, 2013 | College Massachusetts, US | Cross-sectional | 47 | No mean/median reported. Age categories: <18, 18-19, 20-21, 22-23 and >23). | 25.85(55) | Where behavior matches prescription, adherence=1, where it deviates, adherence=0. | The concordance between how often individuals were instructed to take their medication and how often they actually took it | 15(32) |
| Britto et al., 2017 | Cincinnati Children's Hospital Medical Center Ohio, US | longitudinal crossover study | 64 | 17.3 | 53 (82.8) | The no. of medication doses taken each day divided by the no. of prescribed doses taken each day. | Electronic monitoring: SmartInhaler | Average adherence rate: 12.5% |
| D'Souza et al., 2010 | Medical and pharmacy claims data of H-E-B employees and their dependents US | Quasi-experimental, intervention versus control group | 764 | 27.4 | 396 (51.83) | MPR ranges from 0%, indicating no adherence, to 100%, indicating perfect adherence. | Medication possession ratio (MPR); (sum of total days' supply of medication for all prescriptions, except the last prescription/ duration of therapy (ie, total no. of days from the first fill date to the last fill date) | Average MPR: 49.05% |
| Delea et al., 2008 | Integrated Healthcare Information Services (IHCIS) US National Managed Care Benchmark Database US | Retrospective cohort | 2269. ICS+Montelukast group, I.e. group with appropriate age:420 | 21.7 (18.0) | 184(43.8) | | Refill rate and MPR | Refill rate: 3.04(2.48). MPR: 37.7(25.9). |
| Dima et al., 2017 | Primary care/pharmacy | Prospective | 902 | 21.86(10.83) | 426(47.2) | Taking adherence:(% | Medication Intake Survey- | Median taking |

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|---|---|---|---|---|---|---|---|---|
| | records France and UK | cohort | | | | of prescribed doses taken). Correct dosing: (% of treatment days when the patient took the correct no. of doses. Drug holidays: 7/7+ consecutive days with no use. Therapeutic coverage: proportion of days with active medication. Overuse: proportion of medication taken/ prescribed quantity | Asthma (MIS-A) | adherence for 1 week, 1 month and 4 months: 85.71%. Mean % of adherent patients for 1 week, 1 month and 4 months = 31.24% |
| Erickson et al., 1998 | Clinical pharmacy Michigan, US | Pre-post | 6 | 25.67 | 3 (50) | A section score of 1/1+: nonadherence. A score of 4: perfect adherence; 0: perfect nonadherence | The Asthma Self-Reported Medication Compliance Assessment questionnaire | Inhaled Medication Score (Mean): 2.7 |
| Guenette et al., 2015 | Family medicine group (FMG) Quebec, Canada | controlled pragmatic clinical trial | 349. Intervention group, I.e. group with appropriate mean age: 108 | 28.44 (11.06) | 57 (52.8) | 1) Morisky Medication Adherence Scale (MMAS-4). 'No' to all questions: good adherence, i.e. lower score=lower adherence. 2) MPR >75%: adherent. Higher score=better adherence | 1) MMAS-4) 2) MPR | Intervention group (1) MMAS-4 M(SD): 1.98(1.09), (2) MPR M(SD): 19.41(19.17) |
| Jessop et al., 2004 | University of Sussex UK | Quasi-experiment | 78 | 22.9(7.3) | 60 (76.92) | Low adherers: scores ranging from 24-35. Medium adherers: 11-23. High adherers: 5-9 | Self-report | M=17.7(SD=10.2). 16.7% were perfectly adherent. 41.7% scored > midpoint, i.e. relatively low levels of adherence. Low adherers (N=12), medium |

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|---|---|---|---|---|---|---|---|---|
| | | | | | | | | adherers (12), high adherers (12). |
| Joseph et al., 2011 | Public high schools Detroit, Michigan, US | Retrospective | 422 | 15.9(1.1) | 252 (59.8) | Taking medication >4 of last 7 days | Self-report | 143 adherent (27.3%) |
| Kleiger & Dirks, 1979 | The National Jewish Hospital and Research Center (NJHRC) Denver, Colorado, US | Cross-sectional | 100 | According to previous publication: 27.60(14.49) (Kinsman et al., 1978; Kinsman et al., 1973) | 59 (59) | A) over abusers, B) under abusers, C) cyclical abusers (over and under use) and D) compliers | Self-report | Compliers: 46(46%), Cyclical Abusers: 15(15%), Over Abusers: 11(11%), Under Abusers: 28(28%). 54% reported at least one form of non-compliance |
| Koster et al., 2015 | Community pharmacies in the Utrecht Pharmacy Practice Network for Education and Research The Netherlands | Cross-sectional | 182 | 15.0(2.0) | 101 (55.5) | Participants with a MARS score ≥ 23 | MARS | Mean MARS score: 20.3(4.2), range 7-25. 40.9% were adherent |
| Koufopoulos et al., 2016 | Universities, UK | Proof-of-concept RCT | 216 | 28.1 (9.7) | 151 (69.9) | A positive response to any of the SMAQ qualitative questions, >2 doses missed over the past week or >2 days of total non-medication during the past 3 months: nonadherent | Simplified Medication Adherence Questionnaire (SMAQ) | M(SD) SMAQ: 1.45(0.29) |
| Martin et al., 2012 | Homes of urban Midwest Peurto Rican youth US | Cross-sectional | 101. High school cohort, i.e. group with appropriate age: 50 | 16(1) | 29 (58) | | Medication monitor If the monitor could not be fitted, the medication counter no. was recorded | Doser, median (IQR): 0.4 (0.4, 1.0), Counter only, median (IQR): 1.1, Combined median (IQR): 0.7 (0.4,1.1) |
| McIvor et al., 2009 | Medical centres Ontario, Canada | Prospective cohort | 534 | 27.8(19.0) | 301 (56.4) | Nonadherence: taking <80% of the required doses | Self-report | 310 (58.1%) missed 0 doses in the previous two weeks |
| Sadatsafavi et al., | Population database | Retrospective | Total Matched Cohort: 2,064 | 27.43 | 1,083 (52.5) | | 1) PDC. PDC was calculated | 1) ICS component: |

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| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 2013 | British Columbia, Canada | cohort | | | | | separately for ICS and the add-on component, and an overall PDC was calculated as the proportion of days the patient was covered by both ICS and add-on component<br>2) Time on uninterrupted treatment | ICS+LABA group: 0.45 (0.43-0.46), ICS+LTRA group: 0.36 (0.35-0.38). Overall PDC: ICS+LABA group: 0.32 (0.30-0.33), ICS+LTRA group: 0.16 (0.15-0.17).<br>2) By the end of year 1, 9% of ICS+LABA and 3% of ICS+LTRA group, had uninterruptedly refilled their prescription, I.e., 6% of the sample were adherent |
| Wells et al., 2013 | Health maintenance organization Michigan, US | Retrospective cohort | 1,302. Once daily ICS use, I.e. group with appropriate mean age: 221 | 28.2(15.8) | 113 (51.1) | Adherence was examined as both a continuous and a dichotomous measure (i.e. ≤75% vs >75%). | Electronic prescription data<br>Adherence: (no. of days' supply for each fill/ total no. of days between the present and subsequent ICS fill | (1) Mean(SD): 61(34),<br>(2) >75%, No.(%): 90(40.7) |
| Williams et al., 2010 | Health maintenance organization Michigan, US | Cluster-randomized trial | 2,698 | 27.8 | 1490 (55.23) | | No. of days supply: (canister size/the dosage info) | M(SD): Intervention: 25.6 (37.3), Control: 27.7 (38.5) |
| Marks et al., 2000 | Population healthcare database New South Wales, Australia | Cross-sectional | 1,372 | Subgroup range: 16-29 | Subjects with preventers (N=740), Female: 307 (41.5) | Adherence: used preventer on most/all days in the preceding month | Self-report | 37.8% of 16-29 yearr subgroup were adherent |
| Backer et al., 2017 | Respiratory Outpatient Clinic, Bispebjerg Hospital Copenhagen, Denmark | Retrospective cohort | 300. Verified asthma group, i.e. group with appropriate age: 111 | 30.4(15.9) | 30.4(15.9) | 1) ≥ 2 redeemed prescriptions | 1) No. of redeemed prescriptions of controller medication<br>2) PDC | 1) No prescription filled: 27 (27.6), Filled ≥ 1: 71 (72.4), Filled ≥ 2: 48 (52.3), Filled ≥3: 41 (36.9)<br>2) PDC: 88.3% |
| Mattke et al., | Medstat Marketscan database | Retrospective | 12476 | Median: 23 | 6363 (51) | | MPR<br>Patients were | MPR: Quartile 1: |

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| 2010 | Boston, Massachusetts, US | cohort | | | | | grouped into quartiles based on MPR. | 7%, Quartile 2: 14%, Quartile 3: 22%, Quartile 4: 54%, Median: 15%. |
| Sadatsafavi et al., 2014 | Healthcare databases of British Columbia, Canada | Nested case-control cohort study | 127081 | 28.1(10.3) | 81,078 (64) | Regular exposure: at least 1 dispensation in each of the four-month periods in the year before the index date. Irregular exposure: at least 1 dispensation in the year before the index date. No exposure: no dispensation in the year prior to the index date | Pharmacy records | ICS+LABA: Regular exposure: 180(5.4%), Irregular exposure: 585(17.6%), No exposure: 2554(77.0%). ICS alone: Regular exposure: 354:(10.7%), Irregular exposure: 1483(44.7%), No exposure: 1482(44.7%). Overall, 4.4 and 12.2% were regularly exposed to ICS+LABA and ICS alone |
| Makhinova et al., 2015 | Texas Medicaid US | Retrospective cohort | 32172 | 15.0 (14.5) | 15,503 (48.2) | Adherent: PDC ≥50%, nonadherent: <50% | PDC Continuous and categorical measures were used | PDC ≥ 80%: 1,332(4.1%), ≥70%: 2,200(6.8%), ≥60%: 3,338(10.4%), ≥50%: 4,792(14.9%). M(SD): 32.2(19.7) |
| Rhee et al., 2018 | Community venues and clinics New York, US | Cross-sectional | 373 | 14.68(1.94) | 186(50) | | 1) MARS 2) Self-report | 1) MARS, M(SD), range: 12.73 (4.09), 4-20. 2) Missed medication days in 2 weeks, M(SD), range: 3.16 (4.43), 0-14. |
| Kosse et al., 2019 | Pharmacies Utrecht, The Netherlands | Cluster RCT | 234 | 15.1(1.9) | 123(52.6) | Adherence: MARS score ≥23 | MARS | 88(37.61%) were adherent |

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| | | | | | | Poor adherence: MARS score ≤19 | | (≥23). 76(32.48%) had poor adherence (≤19), MARS M(SD): 15.6(3.1). MARS M(SD) Control group: 20.4(4.0), Intervention group: 20.4(3.9). |

Table 2. Summary of studies reporting predictors of adherence to ICS

| Reference | Setting | Design | Sample | Age M(SD) | Gender: Female N (%) | Predictor(s) assessed | Predictor(s) measure(s) | Significant predictor(s) |
|---|---|---|---|---|---|---|---|---|
| Axelsson 2013 | Population database West Gothia, Sweden | Cross-sectional | 216 | 22(1) | 138(64) | No perceived need<br>Insufficient routines | Responses to 'If I don't take the medication the most common reason is', were grouped into; 'No perceived need' and 'Insufficient routines' | No perceived need accounted for 9.3-12.9% of the variance in non-adherence (*p*=.004) Insufficient routines accounted for 4.6-6.5% of the variance in non-adherence (*p*=.027) |
| Axelsson et al. 2009 | Population database West Gothia, Sweden | Cross-sectional | 268 | 22(1) | 165(61.6) | Negative Affectivity<br>Impulsivity<br>Hedonic Capacity<br>Alexithymia<br>Antagonism | The Health-relevant Personality 5 factor inventory (HP5i) | Impulsivity was associated with low adherence (*r* =-0.187, *p*<.05) Antagonism (*r*= -0.368, *p*<.05) and Alexithymia (*r*=-0.369, *p*< .05) were associated with low adherence in men Antagonism (*r*= -0.379, *p*=.03) and Alexithymia (*r*=-0.354, *p*=.03) correlated with intentional non-adherence in men |
| Brandt & Dickinson, 2013 | College Massachusetts, US | Cross-sectional | 47 | Age categories: <18, 18-19, 20-21, 22-23 and >23 | 25.85(55) | Asthma-specific Attitudes<br>Asthma specific beliefs<br>Risk tolerance<br>Time preference | Attitudes: Self-report<br>Attitudes and beliefs: self-report<br>Time preference: questions about whether they would like to be paid X amount of dollars in 6 months or $50 in 7 months. A | Financial need (*β* =-3.12, *p*=.03), being risk averse (*β* =-1.37, *p*=.02) and having a low time preference (*β* =-.85, *p*=.03) predicted adherence. Having concerns about the medication made a participant less likely to adhere (*β* =-4.03, *p*=.04). |

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| | | | | | | | lower category represents a lower time preference Risk tolerance: questions in which to choose between 2 options; A was the safest, B was an increasingly attractive but risky gamble. A higher category represents higher risk tolerance. | Feeling embarrassed about taking medication (*β* =-1.41, *p*=.39) and feeling that asthma is unfair (*β* =2.39, *p*=.09) did not predict adherence. |
| Guenette et al., 2015 | Family medicine group Quebec, Canada | controlled pragmatic clinical trial | Overall: 349. Intervention group, I.e. group with appropriate mean age: 108. | 28.44 (11.06) | 57 (52.8) | 54 intermediate factors identified from the PRECEDE phase of the PRECEDE-PROCEED approach; 19 predisposing factors, 23 enabling factors, 4 reinforcing factors, 1 lifestyle factor and 7 environmental factors | Self-report | |
| Jessop et al., 2004 | University of Sussex, UK | Quasi-experiment | 78 | 22.9(7.3) | 60 (76.92) | Emotional representations of asthma: asthma symptom words. | The asthma Stroop task. Three sets of words were used as stimuli: asthma symptom words (breathless, wheeze, cough, tired, mucous, phlegm, asthma, and gasp), general negative words and neutral words | There was a main effect of adherence group *F*(2,18)=6.94, *p*=.039 Low adherers showed greater interference for the asthma stimuli than medium adherers |
| Kleiger & Dirks, 1979 | The National Jewish Hospital and Research Center (NJHRC), Denver, Colorado | Cross-sectional | 100 | According to previous publication: 27.60(14.49) (Kinsman | 59 (59) | Panic-fear (P-F) | 20 P-F | Participants high on PF were more likely to be cyclical abusers than moderates ($\chi^2$ =2.77, *df*=1, *p*<.10) or lows |

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| | | | | et al., 1978; Kinsman et al., 1973) | | | | ($\chi^2$ =5.87, *df*=1, *p*<.02) or combined moderates and lows ($\chi^2$ =4.65, *df*=1, *p*<.04) Participants low on PF were more likely to be under abusers than moderates ($\chi^2$ =3.15, *df*=1, *p*<.08) or highs ($\chi^2$ =7.07, *df*=1, *p*<.01) or combined moderates and highs ($\chi^2$ =7.11, df=1, *p*<.01) |
| Koster et al., 2015 | Community pharmacies in the Utrecht Pharmacy Practice Network for Education and Research, The Netherlands | Cross-sectional | 182 | 15.0(2.0) | 101 (55.5) | Patients' perceptions about their ICS Perceived necessity of and concerns Asthma Control Knowledge about asthma medication use Knowledge about disease | Beliefs about Medicines Questionnaire-specific (BMQ) Asthma Control Questionnaire (ACQ) Self-report | Well-controlled asthma was associated with higher adherence (*p*=.02), Stronger necessity beliefs was associated with higher adherence (*p*=.04), Indifferent users were more non-adherent compared to accepting users (*p*=.01), Having sufficient knowledge about medication was associated with better adherence (*p*=.03) |
| Martin et al., 2012 | Homes of urban Midwest Peurto Rican youth US | Cross-sectional | Total: 101, high school cohort, i.e. group with appropriate age: 50 | 16(1) | 29 (58) | Psychosocial variables: Depression Stress. Demographic variables: age Sex race/ethnicity Peurto Rican acculturation Education Insurance | Depression: The Patient Health Questionnaire 9 Stress: Life Events Checklist Acculturation: self-report | No psychosocial or demographic variables were associated with adherence |
| Wells et al., 2013 | Health maintenance organization Michigan, US | Retrospective cohort | Total: 1,302, Once daily ICS use, I.e. group with appropriate mean age: 221 | 28.2(15.8) | 113 (51.1) | ICS dosing regimen Sex Race/ethnicity Age Asthma severity | ICS dosing regimen: once vs ≥2 times daily dosing, Race/ethnicity: African American, white individuals, Age: <18, ≥18, Asthma severity: low | Once daily dosing was associated with a 19.3% increase in adherence (*p*≤.001) Women (p= .036) and African Americans (*p*≤.001) had lower adherence Age (*p*≤.001), asthma severity (*p*=.02) and other |

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| | | | | | | | and low-moderate combined, moderate-severe and severe combined | controller medication use (*p*=.02) were positively associated with adherence<br>Once daily dosing was associated with an increased likelihood of achieving >75% adherence as compared with 2/2+ times (OR, 3.28; adjusted OR, 3.51; *p*<.001 for both)<br>Once daily dosing was associated with greater adherence when compared with 2/2+ times in the following subgroups: sex, race/ethnicity, age and asthma severity (*p*<.01) |
| Rhee et al., 2018 | Community venues and clinics<br>New York, US | Cross-sectional | 373 | 14.68(1.94) | 186(50) | Social cognitive theory factors: Self-efficacy (SE), Outcome expectations, Barrier perceptions | Self-report | SE was associated with adherence (0.426, *p*<.001)<br>Higher SE predicted higher adherence<br>SE was not associated with missed doses<br>Outcome expectations were not associated with adherence or missed doses<br>Barrier perceptions were associated with adherence (-.568, *p*<.001) Higher barrier perceptions predicted lower adherence<br>Barrier perceptions were not associated with missed doses<br>After adjusting for the other cognitive measures and demographics: Higher SE predicted a lower no. of missed doses (-.621, *p*=.006)<br>Outcome expectations were not associated with adherence or missed doses<br>Lower barrier |

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| | | | | | | | | perceptions predicted higher adherence (-.519, *p*<.001). After adjusting for all variables, females had worse adherence (*p*=.053) |

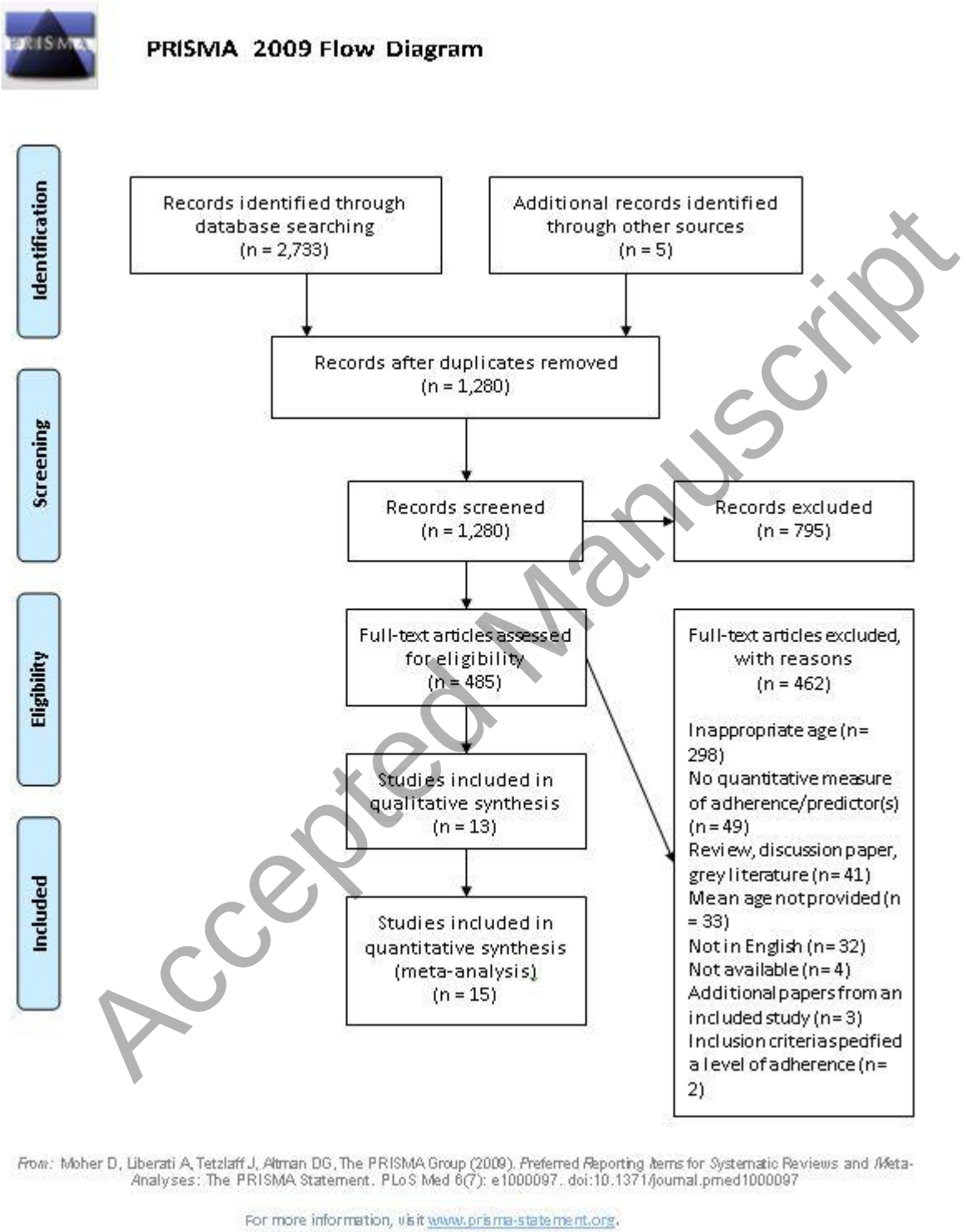


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Figure 1. PRISMA flow diagram

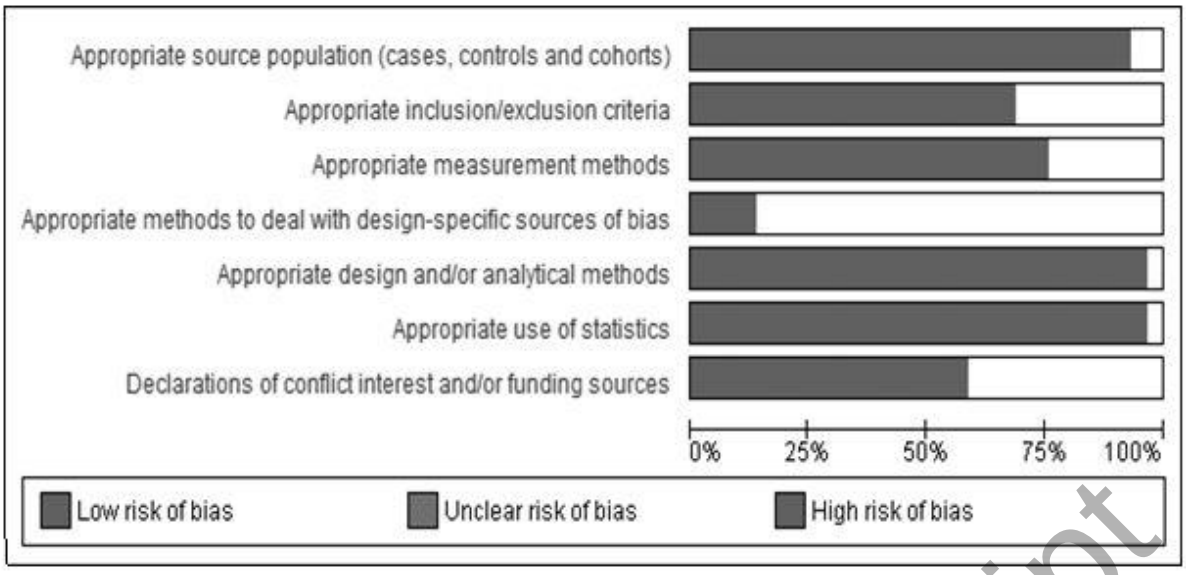


Figure 2. Risk of bias graph.

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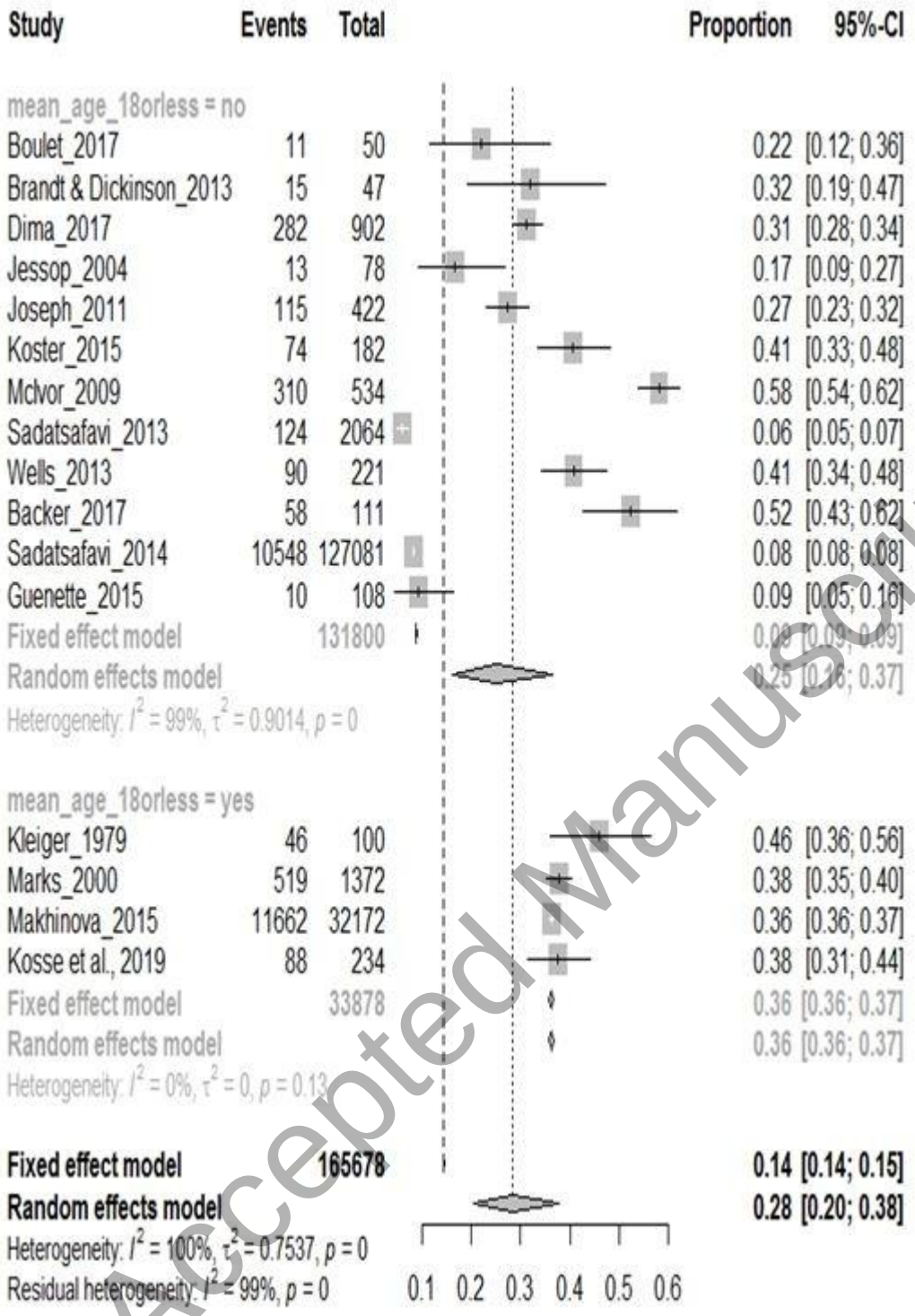


Figure 3. Forest plot of meta-analysis by age.

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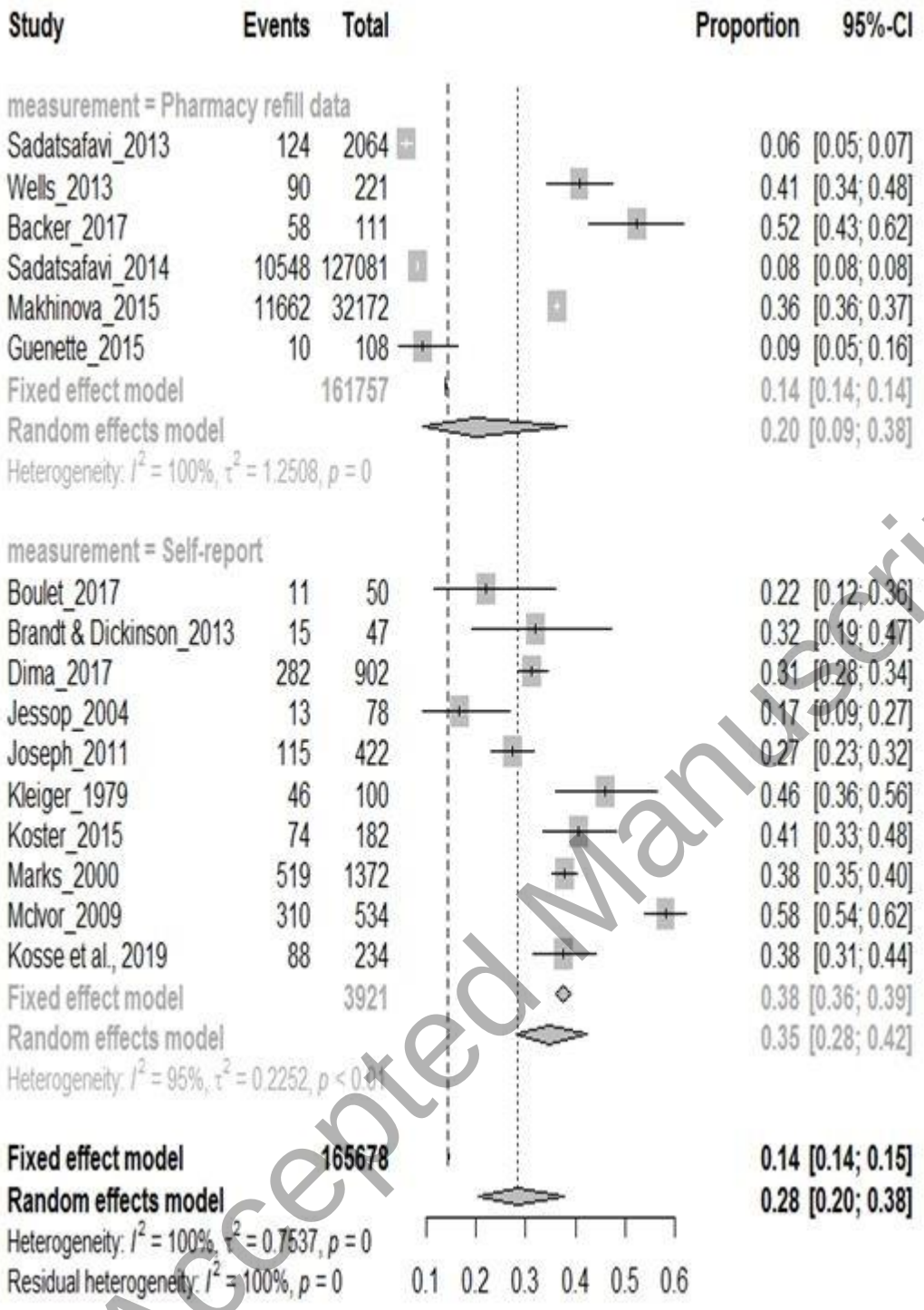


Figure 4. Forest plot of meta-analysis by adherence measure.

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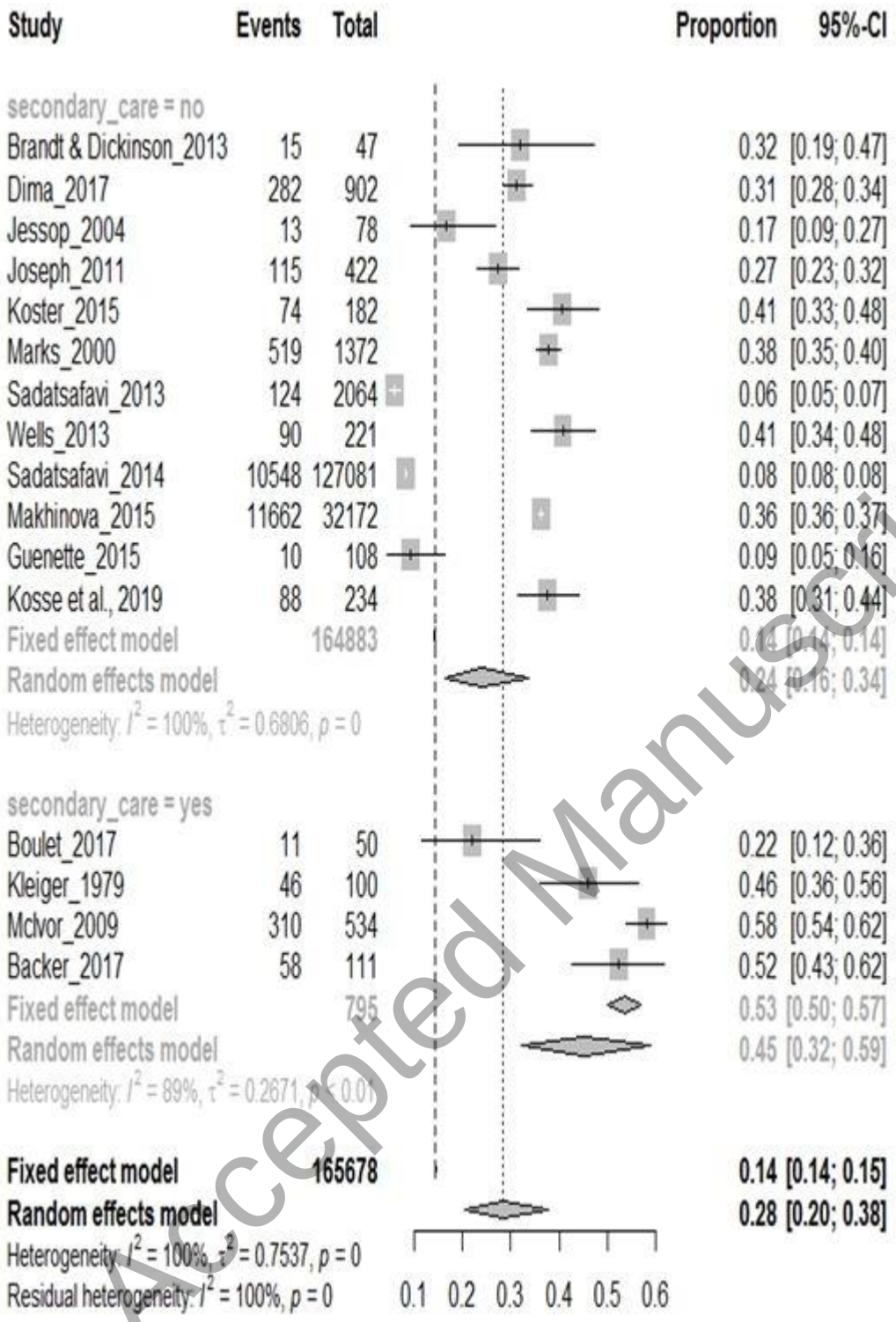


Figure 5. Forest plot of meta-analysis by method of recruitment.

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