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Master's Dissertation

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Title:

**Analysis of Medication Adherence among Children and
Young Adults with Cardiovascular Disease using the
COM-B Model of Behavior Change: A Scoping Review**

21MN042

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Abstract

Background: One of the medical concerns is medication adherence which is an essential issue in clinical practice. Even though medication adherence studies are abundant in medical research, studies about and integrated knowledge regarding medication adherence in children and young adults with cardiovascular disease are scarce. This study aimed to identify medication adherence rate and factors associated with medication adherence and explore its consequences on children and young adults with cardiovascular disease.

Methods: This scoping review was conducted in accordance with the JBI methodology for scoping reviews and would be reported following the Preferred Reporting Items for Systematic reviews and Meta-analyses extension for scoping reviews (PRISMA-ScR) checklist. The following electronic databases were searched: PubMed, CINAHL, and PsycInfo. For additional articles, reference lists and citations of eligible studies for full-text review will be examined. Moreover, Google Scholar will also be searched for relevant articles with free-hand search. The medication adherence rate and outcomes were synthesized and reported in a narrative summary. The COM-B model of behavior change was used to guide the analysis of the factors associated with medication adherence.

Result: Thirteen studies met the eligibility criteria. Two categories were found in this scoping review, including injectable medication adherence, and oral medication adherence. Twelve studies reported the medication adherence rate. Most of the participants were injection non-adherence but adhered to oral medication. 46 factors were reported in ten studies (e.g., understanding the disease, experiences of childhood maltreatment, etc.). There was no factor reported under automatic motivation. Only one study reported the outcomes for oral medication non-adherence, which were graft rejection, risk of mortality, and death.

Conclusion: Factors were mapped and identified that required further research. Studies regarding the outcomes of medication adherence were scarce. Moreover, The COM-B model of behavior change was recommended for further research, practice, and policy development for easy understanding, and implementation.

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Chapter I

Introduction

1. Background and rationale

Cardiovascular disease is one of the five leading causes of death globally and in Thailand (Institute for health metrics and evaluation, 2019). Moreover, it is also one of the five causes of death among adolescents in the United States (Miniño, 2010). The prevalence rate, of congenital heart disease (CHD) rate in the United States, Metropolitan Atlanta, was 86.4 per 10,000 live births from 2000 to 2005 (Bjornard et al., 2013). For Thailand, the data about the prevalence rate of congenital heart disease is scarce. In the Northeastern region of Thailand, the prevalence rate of congenital heart disease and rheumatic fever/rheumatic heart disease (RF/RHD) was 1.2 and 0.23 per 1,000 live births, respectively (Chaikitpinyo et al., 2014). For the mortality rate, in the United State, the mortality rate of heart disease is 211.5 deaths per 100,000 which is the highest mortality rate in the USA (Centers for disease control and prevention, 2019). Unfortunately, some of them have a worsening prognosis even if they received appropriate treatment and medication. One of the factors influence prognosis is adherence (Neiman et al., 2017). Therefore, adherence is an important variable for maintaining their health, especially medication adherence.

Adherence was defined by the World Health Organization (WHO) in 2003. That is defined as personal behavior which corresponds with healthcare provider recommendations (Sabaté, 2003). Therefore, medication adherence is taking medicine following health care provider recommendations. There is some evidence that shows a correlation between medication adherence and outcomes in an adolescent with heart disease. Firstly, the risk of mortality was dramatically raised to 23% after medication nonadherence at 1 year in adolescents with a heart transplant. Furthermore, it will rise to 33% within 2 years after the first nonadherence has been reported (Oliva et al, 2013). Secondly, the prognosis is

significantly related to medication adherence. Good oral medication adherence has a low risk of infection in children with rheumatic fever (Amarilyo et al., 2019). Thirdly, the health care cost was approximately 8 to 10 billion dollars yearly. That was associated with adherence problems and drug-related problems (McLean, 2007). Hence, medication adherence is an essential issue that must be concerned not only for health care providers but also for their families and relatives.

For medication adherence barriers, World Health Organization has categorized five dimensions of medication adherence barriers including, socioeconomic, health care team and health system, therapy, condition, and patient (Sabaté, 2003). On the other hand, Müller et al. have reviewed the literature about variables associated with medication-related non-adherence. They classified a barrier to adherence into four groups, Medication-related barrier (the complexity of medication regimen and fear of side effects, health care system-related barrier, patient-physician relationship, etc.), patient-related unintentional barrier (depression, forgetfulness, etc.), and patient-related intentional barrier (general attitudes towards the treatment, health beliefs, etc.) (Müller et al., 2015). Moreover, there is some article that studies the adherence barrier of rheumatic heart disease. There are four variables such as long-distance from the treatment setting, lack of money, unaffordability, and inconvenient work schedule (Adem et al. 2020).

From an empirical view as an ICU nurse, adolescents and young adults with cardiovascular disease experience outpatient visits due to a lack of adherence. In 2017, 70% of adolescents and young adults with rheumatic heart disease were a very low adherence rate with the proportion of the days covered (PDC) that 80% of participants' PDC was less than 0.8 (Engelman et al., 2017). Besides, I have an experience with patients who had a poor prognosis due to a lack of adherence. They were hospitalized with clinical worsening. In heart transplantation, a study in the United States found that 56% of non-adherence died within 2 years after heart transplantation. Moreover, one of the factors is the age range from 12 to 17 years old (Oliva et al., 2013). Sometimes, the causation

of nonadherence is not only coming from the patient's variables. It often comes from health professionals underestimating and denying it (McLean, 2007). Consequently, it is essential issue to find out the variables of barriers to medication adherence, especially for adolescents and young adults. At this age, adolescents and young adults have unstable development and hormones that were influenced by the transition period. That relates to body image, poor coping, risk-taking, etc. in adolescents and young adults and has a negative effect on medication adherence (Ringewald, 2001). As aforementioned, the risk-taking behavior of adolescents and young adults should be concerned and prevented to decrease the outcomes from medication non-adherence such as poor prognosis, increase risk of mortality, etc. So, the applicable model is important for healthcare professionals to guide, and create an appropriate intervention for maintaining medication adherence in children and young adults.

The COM-B model of behavior is an applicable model for the study of behavior and behavior changing. There are three components including, capability, motivation, and opportunity (West & Michie, 2020). This model was applied to improve patients' behavior. It can be successfully applied to analyze patients with hearing loss behavior (Barker, 2016). For medication adherence, Mishra and his colleagues (2021) explore barriers to medication adherence in patients with cardiovascular disease in low- and middle-income countries using the COM-B model (Mishra et al., 2021). Moreover, it is also a useful model for understanding the barriers and facilitators to chlamydia testing in young people (McDonagh et al., 2018). Therefore, it is shown that the COM-B model is a useful model for the study of adherence.

Even though studies regarding medication adherence in children and young adults with cardiovascular disease are fruitful. However, A preliminary search on PubMed, Cochrane Database of Systematic Review, and JBI Evidence Synthesis was conducted and no current or underway systematic review or scoping review on this topic was identified. Hence, this scoping review aims to identify medication adherence rate and factors associated with medication adherence and explore its consequences on children and young adults with

cardiovascular disease.

2. Significance of the study

This research will help identify medication adherence rates by integrating evidence from eligible original research that would be useful for healthcare professionals to understand and shed light on a medical problem. Moreover, study findings can help healthcare professionals to understand the potential causes of medication non-adherence and can be generalized to other diseases in children and young adults. Furthermore, clarifying these important factors will be useful in creating a behavioral intervention strategy at the individual and policy levels to help medication non-adherence. This is apparently the first scoping review to clarify medication adherence factors among children and young adults with cardiovascular disease and analyze them using the COM-B model of behavior change.

3. The scope of the study

This study aims to identify the medication adherence rate, and factors and explore the outcome of medication adherence and non-adherence in children and young adults with cardiovascular disease by using the COM-B [capability (C), opportunity (O), and motivation (M) factors for changing behavior (B)] model for behavioral change. The PCC (Population, Concept, Context) framework will be used to guide eligible criteria. We will include studies that researched cardiovascular disease patients aged under 24 years old (Population), medication adherence (Concept), and hospital setting (Context). All qualitative, quantitative, and mixed-method study designs will be included in this review. The following filters will be applied to determine inclusion: full-text availability, English language, human studies, and date restriction from 2000 to 2022.

4. The objective of the study

- a) To identify medication adherence rates in children and young adults with cardiovascular disease
- b) To identify medication adherence factors in children and young adults

with cardiovascular disease

- c) To explore the outcome of medication adherence and non-adherence in children and young adults with cardiovascular disease.

5. Research question

1. What are the medication adherence rates, and factors in children and young adults with cardiovascular disease?
2. What are the outcomes of medication adherence and non-adherence in children and young adults with cardiovascular disease?

6. Conceptual framework

The conceptual framework was based on the COM-B model of behavior. The COM-B model of behavior was developed from existing behavioral theories and the consensus of behavioral theorists in the United State. It is comprehensive and applicable to all volitional behavior (Michie et al., 2011). The COM-B model was hypothesized as the interaction between three components causes the performances of behavior (Jackson et al., 2014). Three components are capability, motivation, and opportunity included (West & Michie, 2020). Each component can influence behavior directly. Moreover, capability and opportunity can influence motivation and affect behavior. In addition, this model is dynamic circulation. The behavior can influence capability, opportunity, and motivation as well (Jackson et al., 2014). The detail in each component was described as follow,

Capability is an attribute of a person that together with opportunity makes a behavior possible or facilitates it. In this component, there are two subcomponents psychological, including psychological capability, which was defined as the capability that involves a person's mental functioning (e.g., understanding and memory); and physical capability, which was defined as the capability that involves a person's physique, and musculoskeletal functioning (e.g., balance and dexterity) (West & Michie, 2020).

Opportunity is an attribution of an environment system that together with capability makes a behavior possible or facilitates it. In this component, there are

two subcomponents, including physical opportunity, which was defined as the opportunity that involves inanimate parts of the environment system and time; and social opportunity, which was defined as the opportunity that involves other people and organizations (e.g., culture and social norms) (West & Michie, 2020).

Motivation is an aggregate of mental processes that energize and direct behavior. In this component, there are two subcomponents, including reflective motivation, which was defined as the motivation that involves conscious thought processes (e.g., plans and evaluations); and automatic motivation, which was defined as motivation that involves habitual, instinctive, drive-related, and affective processes (e.g., desires and habits) (West & Michie, 2020).

Behavior is individual human activity that involves the coordinated contraction of striated muscles controlled by the brain (West & Michie, 2020). In this study, the behavior was directly focused on medication adherence.

Chapter II

Literature Review

This study aimed a.) to identify medication adherence rates b.) to identify medication adherence factors C.) to explore the outcome of medication adherence and non-adherence in children and young adults with cardiovascular disease by analyzing using the COM-B [capability (C), opportunity (O), and motivation (M) factors for changing behavior (B)] model for behavioral change. Hence, the literature was reviewed regarding the purpose of this study. As follows,

1. Cardiovascular disease in children and young adults
 2. Medication adherence in children and young adults
 3. Challenge in care in medication adherence in children and young adults with cardiovascular disease
 4. COM-B model of behavior change
- 1. Cardiovascular disease in children and young adults**

Commonly, heart diseases in children and adolescents were congenital heart diseases (CHD) and acquired heart diseases (AHD), approximately 1.0% of the population (McBride et al., 2020). So, this literature review in this section focused on congenital heart diseases (CHD) and acquired heart diseases (AHD).

Congenital heart diseases

Congenital heart disease was defined as developmental anomalies present at birth that are due to an embryonic malformation in the structural development of the heart and major blood vessels (Smith, 2001). It would present in about 9 of every 1000 live-born children (Puri et al., 2017). There were 35 types of congenital heart disease occurring alone or in combination (Smith, 2001). The severity of the disease could be ranged from asymptomatic to life-threatening because of many diseases with variable pathophysiology (Rohit & Rajan, 2020). There were two types of congenital heart diseases, including acyanotic congenital heart disease, and cyanotic congenital heart disease (Anagnostopoulou, 2023). For acyanotic congenital heart disease, most patients did not display a change in skin

tone in cyanosis. The symptom of cyanosis would appear if the oxygen saturation was decreased below more than 85% (Kannan, 2020). Acyanotic congenital heart diseases were atrial septal defects, ventricular septal defects, patent ductus arteriosus, etc. Cyanotic congenital heart disease was a serious condition of congenital heart disease. It affected 3-4% of newborns and needed investigation and emergency treatment. The etiology varied and could be classified as cardiac and non-cardiac causes. Cyanotic congenital heart diseases were Tetralogy of Fallot, transposition of the great arteries, etc. (Rohit & Rajan, 2020).

Overall, the mortality rate of congenital heart disease had been declined since 1990 by 34.5%. Unfortunately, the prevalence rate was not (Smit-Fun & Buhre, 2019). The one-year, five years, and ten years survival rate for congenital heart disease was 87%, 85.4%, and 81.4%, respectively (Best & Rankin, 2016). For survival rate and body weight, children who were born with term and normal weight had a survival rate of 96.3% (Best et al., 2017). The previous study found that socioeconomic status (SES) played an important role in the survival rate among children with congenital heart disease (Xiang et al., 2019).

Caring for congenital heart disease patients had several concerns, including compliance issues, psychosocial issues, neurodevelopmental issues, etc. Most of the patients needed long-term care and follow-up. Lack of knowledge, lack of symptoms, and lack of financial resources influenced the loss of follow-up. That would increase the risk of mortality later. For psychological issues, most of the patients had to confront and cope with heart disease. That might impact their mental health. Moreover, children with congenital heart disease had to face self-identity, self-esteem, and self-image developmental issues because of chronic illness, especially adolescents. Regarding neurodevelopment, children with congenital heart disease were at risk for neurodevelopmental disorders such as learning difficulties, attention-deficit hyperactivity disorder, etc. (Gupta, 2014). Hence, it was important for healthcare providers to assess the risk factors regarding non-adherence, mental illness, neurodevelopment disorders, etc. to decrease the risk of mortality and increase the quality of life among children with congenital heart disease.

Acquired heart diseases

Acquired heart disease which was an uncommon disease in children affecting the heart and vessels and appeared after birth (Bezold & Bricker, 1994; Wilson et al., 2014). The causation of acquired heart disease was various such as infection, metabolic, nutrition, etc. The common acquired heart disease included rheumatic fever/ rheumatic heart disease, myocarditis, and pericardial disease (Wilson et al., 2014). Rheumatic fever/ rheumatic heart disease contributed to morbidity and mortality in developing countries (Arvind & Ramakrishnan, 2020). Rheumatic fever/ rheumatic heart disease was reported by the global review that 15.6 million prevalent cases, 282,000 incident cases, and 233,000 deaths annually (Wyber et al., 2014). Besides, a previous systematic review and meta-analysis conducted on children and adolescents with rheumatic heart disease in endemic regions found that the pooled prevalence of rheumatic heart disease detected by cardiac auscultation was 2.9 per 1000 people and by echocardiography was 12.9 per 1000 people (Rothenbühler et al., 2014). However, a previous study found that the data from low – and middle-income countries was inadequate even if they had the highest burden from rheumatic fever/ rheumatic heart disease. Moreover, most of the studies regarding the prevalence or incidence of Rheumatic fever/ rheumatic heart disease were conducted in the urban area instead of the rural area which might be a higher prevalence rate than in the urban area (Musa et al., 2017).

Most of the rheumatic fever/ rheumatic heart diseases had to receive secondary antibiotic prophylaxis to prevent disease progression (Arvind & Ramakrishnan, 2020). However, low- and middle-income countries do not still have an effective program for secondary antibiotic prophylaxis because of a lack of human resources, facilities, financial resources, etc. which might be life-threatening for rheumatic fever/ rheumatic heart disease patients (Musa et al., 2017). Moreover, rheumatic fever/ rheumatic heart disease had a lot of complications such as arthritis, Sydenhams chorea, etc. That would influence the patients to pain, mental illness, death, etc. So, healthcare providers should carefully assess drug adherence, complications of the disease, mental health, etc.

to improve quality of life, decrease mortality rate, and prevent life-threatening events.

2. Medication adherence in children and young adults and challenge in care

Adherence was defined as personal behavior which corresponds to healthcare professional recommendations (Burkhart & Sabaté, 2003). Medication adherence was a major concern in pediatrics and public health (Hoegy et al., 2019). Medication adherence has been shown to be a problem in several long-term conditions in both children and adults (Pearce & Fleming, 2018). Medication adherence rate in children was a wide range. 63% of children and adolescents with chronic illness are prescribed medication but 50% to 88% of them are non-adherence (McGrady & Hommel, 2013). According to a previous systematic review, in children with organ transplants, medication adherence was lower than 80% in two-thirds of the studies (64%), ranging from 22% – 97% (Hoegy et al., 2019). So, referring to existing evidence, we can assume that most of them were non-adherence. For the medication adherence measurement, various methods were applied to assess the adherence rate in pediatric patients such as pharmacy refills, self-report, electronic monitoring, questionnaires, etc. (Al-Hassany et al., 2019; McGrady & Hommel, 2013; Hoegy et al., 2019).

Regarding medication adherence factors, there was a large amount of evidence that found several factors influencing medication adherence in children and young adults. According to a previous study, a systematic review study on medication adherence in children and adolescents with severe mental illness found that medication non-adherence was associated with illness severity, substance use, etc. (Edgcomb & Zima, 2018). Moreover, a systematic review conducted on children with sickle cell disease found that factors associated with medication adherence were not only influenced by individuals but also by environments. For instance, they found that insurance problems, difficulty to come to the clinic, etc. were risk factors for the barrier to adherence (Walsh et al., 2014). So, medication adherence is an essential issue for every healthcare professional at every level of the healthcare system to monitor, maintain, and

improve to prevent the outcomes from medication non-adherence that impacted to children's quality of life.

Challenges in care for medication adherence in children and young adults were individual, different backgrounds, different developmental statuses, different medication regimens, etc., especially adolescent and young adults. Commonly, children who had to take medication would be supported by families. Even though they went to school, the school nurse or teacher would be taking an important role in taking care of the ill children. For instance, the school nurse reminded rheumatic heart disease, patients, to take the medication (Mincham et al., 2003). In contrast, the adolescent would change from being dependent on family to be independent. During this period, they would make decisions by themselves (Phillips et al., 2018). Moreover, Adolescents were a vulnerable group to non-adherence because of changes in physical, psychological, and developmental tasks (Salema et al., 2011). Hence, underestimating the adherence, disconnectedness between patients and healthcare providers, psychosocial issues, etc. can influence adolescents to take a risk-behavior such as medication non-adherence, substance use, etc. Therefore, Medication adherence was an essential issue for healthcare providers to consistently assess, monitor adherence, and prevent and decrease the risk factors that might affect medication adherence in children, especially adolescents and young adults.

3. COM-B model of behavior change

The COM-B model of behavior change was the three essential conditions of the center of the behavior change wheel (BCW). It was the 'behavior system' which was composed of three essential conditions for performing the behavior, including capability, opportunity, and motivation (COM-B system) (Michie et al., 2011). It was developed because the previous intervention did not use the available framework for developing the intervention, existing models and frameworks were not comprehensive, describe the dynamic of behavior, lack of factors regarding the system level, coherent, etc. (Jackson et al., 2014; Michie et al., 2011). So, Michie et al. (2011) would like to construct a framework that was comprehensive, coherent, and able to link to an overarching model of behavior.

The process of construction was including a systematic review of the current frameworks, development of the framework, and reliability testing. The COM-B model was developed on the basis of two considerations: 1.) a US consensus meeting of behavior theorists; 2.) a principle of US criminal law dating back many centuries. Hence, Michie et al. (2011) identified three necessary factors to perform the specific volitional behavior, including the skill necessary to perform, a strong intention to perform, and no environmental constraints. At the end of the process, three conditions were included, capability, opportunity, and motivation. The definitions and subcomponents under each component of the COM-B model would be described as follow,

Capability

The capability was defined as the individual capability in terms of psychological and physical capability to engage in activities (Michie et al., 2011). For each subcomponent, the psychological capability was defined as the capability to engage in the necessary thought process (e.g., understanding, memory (West & Michie, 2020), executive function (Jackson et al., 2014)) (Michie et al., 2011). The physical capability was defined as the capability that involved a person's physique, and musculoskeletal functioning (e.g., balance, dexterity, etc.) (West & Michie, 2020).

Opportunity

The opportunity was defined as all factors that were outside the individual that made the behavior possible or prompt it (Michie et al., 2011). In this component, there were two subcomponents, including physical opportunity, and social opportunity. The physical opportunity was defined as an opportunity that involved inanimate parts of the environment and time (e.g., financial, and material resources). The social opportunity was defined as an opportunity that involved other people and organizations (e.g., culture and social norms) (West & Michie, 2020).

Motivation

Motivation was defined as all brain processes that energize and direct behavior, not just goals and decision-making. It included habit, emotion, etc. (Michie et al.,

2011). There were two components under this component, including reflective motivation, and automatic motivation. Reflective motivation was defined as the motivation that involved conscious thought processes (e.g., plans and evaluation). The automatic motivation was defined as motivation that involved habit, instinct, drive-related, and affective processes (e.g., desires and habits) (Michie et al., 2020).

According to West & Michie (2020), the COM-B model had a dynamic within components. Capability and opportunity influenced the relationship between motivation and behavior. The greater capability and opportunity probably influenced the behavior to occur. Besides, capability and opportunity influence a person's motivation to perform the behavior. Logically, adequate capability with sufficient resources would influence belief to perform the behavior. Moreover, behavior possibly feeds back to all three components creating positive or negative feedback. For instance, obese patients were encouraged to exercise. When they perceived that they could do it and had weight loss. They would have more motivation and capability to perform the behavior further.

Limitations of applying the COM-B model for research, and practice

According to the previous study, Whittal et al. (2021) found that there were some challenges in applying the COM-B model of behavior change for intervention. First, they found that it was difficult to make a solid judgment on categorizing the determinants following the COM-B model. For instance, self-efficacy would be categorized under psychological capability in terms of “knowledge or psychological skills, strength, etc.” and could also categorize under reflective motivation in terms of “evaluation about oneself”. They suggested discussing among the research team to find a solution to the disagreement. Second, they found that the COM-B model did not take into account cultural background, age, or other factors. For example, the cultural background would influence a specific behavior such as beliefs, norms, etc. In a previous study, they would like to categorize the belief under social capability. That was in contrast with the guideline from the developer. They would categorize the belief under reflective

motivation. Finally, they categorized it under the reflective motivation following the guideline because they thought “even if culturally influenced, individual evaluation is required to shape the way one attributes illness symptoms”. They suggested that it would be useful to include more terms on the list of relevant behaviors for each of the COM-B model’s components in the guideline.

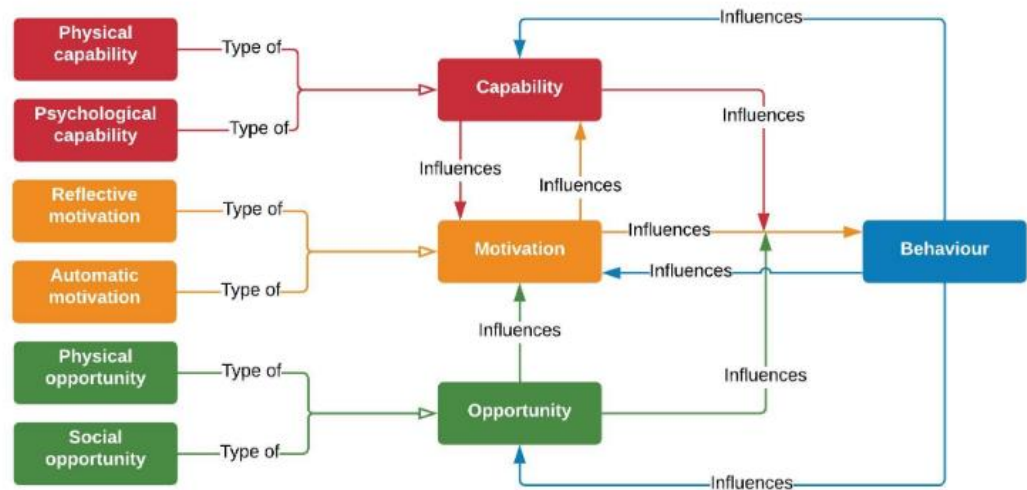


Figure 1, the COM-B model of behavior change. From “A brief introduction to the COM-B Model of behaviour and the PRIME Theory of motivation,” by R. West and S. Michie, 2020, *Qeios*, (doi:10.32388/WW04E6.2.).

Chapter III

Methods

This scoping review was conducted in accordance with the JBI methodology for scoping reviews (Peters et al., 2020) and is reported following the Preferred Reporting Items for Systematic reviews and Meta-analyses extension for scoping reviews (PRISMA-ScR) checklist (Tricco et al., 2018).

1. Protocol and registration

This scoping review was written and drafted following the preferred reporting items for systematic reviews and meta-analyses Protocols (PRISMA-P) (Shamseer et al., 2015). Moreover, it was registered in Figshare (<https://doi.org/10.6084/m9.figshare.21749255.v1>) (Katchamat et al., 2022), an online open-access for researchers to share and preserve data and research that can register scoping reviews.

2. Eligible criteria

The eligible criteria were created following the PCC (Population/Concept/Context) framework guided by the Joanna Briggs Institute (JBI) (Tricco et al., 2018). The detail was described as follows,

Participants

Population was children and young adults aged 1 month to 24 years old, who were diagnosed with any type of cardiovascular disease.

Concept

Concept was the adherence of children and young adults, who were diagnosed with any type of cardiovascular disease, with medication and /or treatment with providing by a healthcare provider. The definition of adherence is a patient behavior in accordance with healthcare professionals' recommendation (Burkhart & Sabaté, 2003), which was defined by any type of medication adherence

measures, including the proportion of days covered (PDC), pill counts, self-report, etc.

Context

Context was a healthcare setting that provides medical care and treatment to children and young adults with cardiovascular disease.

Types of Sources

This scoping review considered any type of original articles of quantitative studies, qualitative studies, and mixed-method studies. The text and opinion paper were not included in this scoping review because they would not be applicable to the research question of this study. Any review articles, including systematic review, meta-analysis, etc., were not included in the data analysis. However, the reference lists were read to find the relevant article.

3. Information sources and search

The Electrical databases, including PubMed, CINAHL, and PsycInfo, were searched by the author under health science librarian guidance. Medical Subject Heading (MeSH) and free search terms (title/ and abstract) were used in this systematic review. The Boolean operators “OR” and “AND” and truncated were used in the search strategy. The keywords were constructed based on the objection of this study which focused on P and C in the PCC framework (Appendix I), as shown in Table 2.

Table 1: lists of the search term in each database

Database	MeSH keywords
PubMed	pediatrics, child, infant, adolescent, young adult, heart disease, cardiovascular disease, drug therapy, medication therapy management, medication adherence, and patient compliance.
CINAHL	pediatrics, child, infant, adolescence, young adult, cardiovascular disease, drug therapy, medication management, medication

	compliance, and patient compliance.
PsycInfo	pediatrics, heart disorder, cardiovascular disorder, drug therapy, and compliance
Databases	Free term Search [Title/ Abstract]
PubMed, CINAHL, and PsycInfo	Pediatric*, paediatric*, child, children, school-age, teen, teenager, adolescent, youth, young adult, heart disease*, cardiovascular disease*, adhere*, compliance, persistence, non-adherence, nonadherence, non-compliance, noncompliance

The reference lists of Included studies and relevant article that doesn't meet eligibility criteria were screened to find out the additional articles. Moreover, the author searched on Google Scholar with free-hand search to find additional articles. The English, full-text availability, and human study were applied as a filter for filtrating study.

4. Selection of sources of evidence

Following the search, all identified citations were saved and imported into EndNote 20 for duplicated article screening and removal (Gotschall, 2021). After duplicated articles were deleted, we collated and exported them to Rayyan, a free web and mobile application for screening eligible studies (Ouzzani et al., 2016). The screening process, the title, and the abstract of articles were independently screened by two or more reviewers following the inclusion criteria. Then, the full-text screening process was performed by two or more independent reviewers adhering to inclusion. The reason for excluding the articles in the full-text screening process was recorded and reported in scoping review. The conflict on screening papers between reviewers was discussed with third reviewers or a person who doesn't have a responsibility to screen those papers. The finding of the search and screening process was reported and presented in scoping review with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension (PRISMA) flow diagram (Page et al., 2021).

5. Data charting process and items

Data was charted by two independent reviewers following the data charting form which was developed by the author in MS Excel under the guidance of an advisor. The data regarding medication adherence rate were charted, including characteristics of included studies, study design, population, setting, definition, measurement, and medication adherence rate. The data regarding medication adherence factors and outcomes were charted in a narrative summary and into each subcomponent of the COM-B model.

6. Critical appraisal of individual sources of evidence

Critical appraisal of an individual source of evidence was not mandatory for scoping review following the JBI methodology on scoping review (Peters et al., 2020). Hence, the critical appraisal was not performed in this scoping review.

7. Synthesis of results

We summarized the characteristics of the included studies: medication adherence measurement, medication adherence rate, medication adherence variables, and clinical outcomes following medication adherence and non-adherence. Two independent reviewers will extract the data and compare it with each other. Disagreement will be solved by a discussion with third reviewers or additional reviewers. Quantitative data will be summarized and described in a narrative summary and analyzed using statistics, including mean, percentage, p-value, etc. To identify the medication adherence factors, the author conducted a thematic analysis of qualitative data. If there is only a qualitative study in review, the theme from each study will be extracted and synthesized with the other. Mixed-method data will be divided and separately analyzed in each type of data. The medication adherence rate was summarized in a narrative summary. The medication adherence rate will be separately summarized in each type of administration. Regarding heterogenic adherence measurement, the adherence rate will be summarized with “adherence” and “non-adherence” based on their definition of adherence. If the studies used the same definition of adherence, the number of

participants would be summarized and narratively described. For a divergent study, it would be used for a narrative summary without combining it with the others. The factors will be listed and categorized following components and subcomponents of the COM-B model of behavior change. If the factors were considered to be in direct relationship with medication adherence, it was marked (+). They would be marked (-) if they were a reverse relationship. If there are some conflicts among evidence, for instance, one piece of evidence indicated that sex was associated with medication adherence but the other showed the contrary result. (\pm) would be used to indicate that factor was an inconsistent relationship. If the factor was extracted from quantitative and not associated with medication adherence, it was marked (NS), which means “not significant”. The medication adherence measures and rates will be summarized in a narrative summary. The medication adherence factors and outcomes will be presented in tabular form and illustrated in a diagrammatic form related to the COM-B model.

Chapter IV

Results

1. Selection of sources of evidence

To identify studies through databases, three biomedical databases were chosen to search studies for scoping review, including PubMed, CINAHL, and PsycInfo. 3585 studies were identified from three databases with MeSH term and free-term search (title/ abstract). In each database, 3016, 439, and 130 studies were identified from PubMed, CINAHL, and PsycInfo, respectively. EndNote 20 was used to detect and remove duplicated studies. After duplicated studies removal, 3535 studies were independently screened by two reviewers with emphasizing title and abstract. 3473 studies were excluded from this scoping review because they were considered not to meet eligibility criteria. So, 62 studies were screened for the full-text screening process. Unfortunately, 10 studies were not retrieved because of the full-text unavailability. Thus, 52 studies were read and screened from the full text by two independent reviewers. In full-text screening, 50 studies were excluded because of eligibility criteria conflicts: 40 studies (different populations); 6 studies (different publication types); 5 studies (different study outcomes). Hence, 1 study was included in this scoping review.

For the identification of additional studies or studies via other methods, 22 studies were identified through the free-hand search method on Google Scholar, a free web search engine. 7 studies were identified from the reference list screening. 1 study was excluded because of the full-text unavailability. Hence, 28 studies were assessed for full-text screening to determine eligibility screening. After the full-text screening, 15 studies were excluded from eligibility, 8 studies (different populations); 7 studies (different study outcomes); and 1 study (different publications). So, 12 studies from additional studies were included in scoping review.

Finally, the final 13 studies were determined and considered to be included studies. In Figure 1, the PRISMA flow diagram 2020 was applied to illustrate the review process for this scoping review.

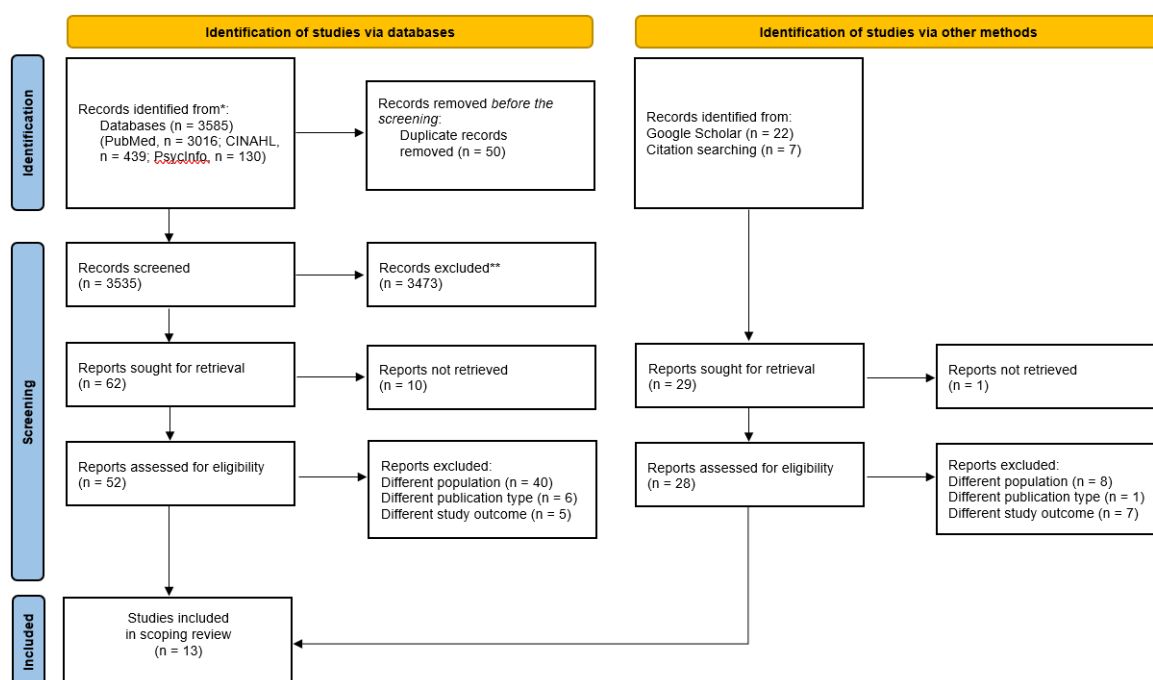


Figure 2, PRISMA flow diagram 2020 for search and screen process in this scoping review

2. Characteristics and results of individual sources of evidence

The Characteristics and results of an individual source of evidence are shown in Table 2. Sample sizes of these included studies ranged from 4 to 2070 participants. The total number of participants from included studies is 3666 participants (1372: rheumatic heart disease; 2294: heart transplantation). Participants' age ranged from 0 to 24 years old. Eight studies studied rheumatic heart disease patients (Adem et al., 2022; Alkan et al., 2022; Kevat et al., 2021; Beaton et al., 2017; Culliford-Semmens et al., 2017; Engelman et al., 2017; Engelman et al., 2016; Balbaa et al., 2015). Five studies studied heart transplantation patients (Wolfe et al., 2020; Grady et al., 2019; Killian, 2017; Olivia et al., 2013; McAllister et al., 2006). The included studies were conducted

in 8 countries. Five out of thirteen studies were conducted in the United States (Wolfe et al., 2020; Grady et al., 2019; Killian, 2017; Olivia et al., 2013; McAllister et al., 2006). Other studies were studies in various countries (two studies: Fiji (Engelman et al., 2017; Engelman et al., 2016), one study: Ethiopia, Turkey, Egypt, Uganda, New Zealand, and Australia (Adem et al., 2022; Alkan et al., 2022; Kevat et al., 2021; Beaton et al., 2017; Culliford-Semmens et al., 2017; Balbaa et al., 2015)). Twelve studies reported regarding medication adherence rate: Eight studies reported injection medication adherence rate (Adem et al., 2022; Alkan et al., 2022; Kevat et al., 2021; Beaton et al., 2017; Culliford-Semmens et al., 2017; Engelman et al., 2017; Engelman et al., 2016; Balbaa et al., 2015), and four studies reported medication adherence rate on oral medication (Grady et al., 2019; Killian, 2017; Olivia et al., 2013; McAllister et al., 2006). For factors, ten studies reported factors associated with medication adherence (Five studies researched injection adherence (Alkan et al., 2022; Kevat et al., 2021; Engelman et al., 2017; Engelman et al., 2016; Balbaa et al., 2015); Five studies researched oral medication adherence (Wolfe et al., 2020; Grady et al., 2019; Killian, 2017; Olivia et al., 2013; McAllister et al., 2006)). Regarding outcomes of medication non-adherence, one study reported poor consequences from medication non-adherence in heart transplantation patients (Olivia et al., 2013).

Author, year	Study design	Purpose of the study	Study setting, Country	Study participants	Measurement	Definition of adherence	Study Finding
Adem et al., 2022	Cross-sectional study	To assess the adherence of RHD patients to secondary prophylaxis and associated factors at multiple hospitals in the Jimma zone, southwest Ethiopia	Four public hospitals in the Jimma zone, Ethiopia	RHD patients on follow-up who fulfilled inclusion criteria (all-age-group, on benzathine penicillin prophylaxis for at least 1 year before the date of interview) (N = 278; aged < 15, n = 47 (18.6%); aged 15 – 24, n = 97 (38.3%); aged > 24, n = 109 (43.1))	Structure questionnaire administered face-to-face Patient record (medical data)	<ul style="list-style-type: none"> • Good adherence when the rate of adherence to secondary prophylaxis was equal to or more than 80% of the expected injections • Poor adherence when the patient missed prophylaxis at least three times per year. 	Medication adherence rate: <ul style="list-style-type: none"> • Good adherence (n = 160 (63%): good adherence; n = 93 (37%): poorly adherent to monthly BPG injections (i.e., missing fewer than and three or more injections in the past year) • For aged < 15: n = 35 (13.8%), good adherence; n = 12 (4.7%), poor adherence • For aged 15-24: n = 60 (23.7%), good adherence; n = 37 (14.6%), poor adherence Factors associated with adherence: Not reported Outcomes: Not reported
Alkan et al., 2022	Cross-sectional study	To investigate the outcomes of psychiatric symptoms and family functions on treatment adherence in children, in addition to sociodemographic characteristics	Celal Bayer University Faculty of Medicine, Department of Pediatric Cardiology, Turkey	Children diagnosed with rheumatic heart disease who were admitted during the study, were previously diagnosed patients, and came to routine control visits. (N = 43)	<ul style="list-style-type: none"> • Sociodemographic data form • Patient's file (information about the disease) • Strengths and Difficulties Questionnaire • Family assessment device 	<ul style="list-style-type: none"> • Regular adherent when the BPG administration was missed less than once a year. • Partially adherent when the BPG administration was missed two-three times per year. 	Medication adherence rate: <ul style="list-style-type: none"> • Regular adherent, n = 31 (72%) • Non-adherent, n = 12 (28%): n = 7 (16.27%), partially adherent; n = 5 (11.63%), non-adherent Factors associated with adherence: <ul style="list-style-type: none"> • Direct relationship - No fear of syringes • Inverse relationship

Author , year	Study design	Purpose of the study and clinical factors related to the disease	Study Country	Study participants	Measurement	Definition of adherence	Study Finding
						<ul style="list-style-type: none"> • Non-adherent when the BPG administration missed four times or more in a year. 	<ul style="list-style-type: none"> - Forgetting to get a prescription and/or take the drug when the time • Not significant - Age - Gender - Living in rural areas and cities - Educational status of parents - Acute rheumatic fever - carditis, acute rheumatic fever - arthritis + carditis coexistence, acute rheumatic fever - carditis coexistence + Sydenham chorea - coexistence - The presence of mild, moderate, or severe carditis and the presence of recurrence - Enough information - lifestyle - Fear of developing adverse effects - Fear of addiction - Lack of health insurance - Difficulties in reaching the drug/hospital - Long-term treatment - Adequate support from the physician - Family assessment device (problem-solving,

Author, year	Study design	Purpose of the study	Study setting, Country	Study participants	Measurement	Definition of adherence	Study Finding
							communication, roles, emotional responsiveness, attention, behavior control, and general functions in the family) - Strengths and Difficulties Questionnaire (attention deficit hyperactivity, behavioral problems, emotional problems, peer problems, and social behaviors) Outcomes: Not reported
Balbaa et al., 2015	Cross-sectional study	To develop future knowledge translation (KT) strategies to improve adherence to RHD prophylaxis, the contextual barriers to optimal adherence in specific populations must be better understood. This study outlines the	Aswan Heart Center, Aswan, Egypt	Asymptomatic RHD children, under the age of 18 (N = 29)	A questionnaire was developed using the three domains outlined by Fishbein, including capability, intention, and healthcare barriers	<ul style="list-style-type: none"> • Optimal adherence to prophylaxis when patients received over twelve injections (> 75%) • Sub-optimal adherence when patients received less than twelve injections in the past year (< 75%) 	<ul style="list-style-type: none"> • Adherent, n = 19 (65.5%) • Non-adherent, n = 10 (34.5%) Factors associated with adherence: <ul style="list-style-type: none"> • Direct relationship - Understanding of the disease - Awareness of the consequences of missing prophylaxis doses • Inverse relationship - Consciously choose to miss an injection appointment • Not significant - Healthcare barriers Outcomes: Not reported

Author, year	Study design	Purpose of the study	Study setting, Country	Study participants	Measurement	Definition of adherence	Study Finding
		development of a tool that will allow for systematic measurement of these barriers, and inform the basis for the design of future KT interventions.					
Beaton et al., 2017	Longitudinal study	To examine the hypothesis that risk factors for the unfavorable outcome can be found through the study of natural history data	The Uganda National Registry, Uganda	Any Children with latent RHD enrolled in the Registry and with at least 1 year of follow-up data (N = 227)	A follow-up assessment is included demographic, socioeconomic, and clinical information	The days of coverage (each injection providing 28 days of coverage) when possible and when not possible, as a percentage of prescribed injections received (benchmark $\geq 80\%$)	Medication adherence rate: <ul style="list-style-type: none"> • Good adherence (the overall adherence (of $\geq 80\%$ days covered or $\geq 80\%$ injection received) was good in 89 children (82.4%) from 108 children. • Overall Mean adherence (SD) = 84.7 (± 0.15) Factors associated with adherence: Not reported Outcomes: Not reported
Culliford-Semmens et al.	Cross-sectional study	To determine adherence to BPG secondary prophylaxis for	Local providers in Counties Manukau, Tairāwhiti,	Children with RHD (N = 57)	Not reported	Overall adequate adherence was defined for each patient as receiving $> 80\%$	Medication adherence rate: <ul style="list-style-type: none"> Adequate adherence ($> 80\%$), n = 39 (68.4%); poor adherence ($< 80\%$), n = 18 (31.6%)

Author, year	Study design	Purpose of the study	Study setting, Country	Study participants	Measurement	Definition of adherence	Study Finding
al., 2017		patients diagnosed with RHD by echocardiographic screening between 2007 - 2012	Bay of Plenty, Northland, and Capital Coast District Health Boards, New Zealand			of injections on time per year	Factors associated with adherence: Not reported Outcomes: Not reported
Engelman et al., 2016	Retrospective cohort study	To investigate the adherence to SAP among young people with RHD diagnosed through echocardiographic screening in Fiji and to investigate factors associated with adherence	All clinics across the four administrative Divisions of Fiji (Central, East, West, and North), Fiji	Children with RHD cases diagnosed through echocardiographic screening (N = 494)	<ul style="list-style-type: none"> Injection book Direct questioning of senior nursing staff 	<ul style="list-style-type: none"> The PDC was calculated by dividing the days-at-risk by the total days observed and subtracting this ratio from 1. The threshold for adequate adherence was defined as $PDC \geq 0.80$ (* Injection of BPG would confer protection for 28 days, after which each subsequent day was considered a "days-at-risk" of developing a subsequent GAS infection and recurrence) 	Medication adherence rate: <ul style="list-style-type: none"> 203 cases that had been commenced on SAP (41.1%) had no injections recorded 171 cases (35.6%) had very poor adherence ($PDC: >0 - 0.39$) 33 cases (6.7%) had adequate adherence ($PDC \geq 0.80$) 31 cases (6.3%) received $\geq 80\%$ of recommended injections Factors associated with adherence: <ul style="list-style-type: none"> Direct relationship Ethnicity (non-iTaukei) Place of residence (Urban) Inverse relationship Time since diagnosis ≥ 1.5 years Not significant screening activity type Outcomes: Not reported

Author , year	Study design	Purpose of the study	Study setting, Country	Study participants	Measurement	Definition of adherence	Study Finding
Engelm an et al., 2017	Cross- sectional study	To understand the health- seeking behaviors and factors affecting adherence to SAP in Fiji, and to identify opportunities and strategies for improving secondary prevention of RHD	Central Division of Fiji, Fiji	All young people with any form of RHD from 2006 to 2013, who were diagnosed on echocardiograph y (N = 101)	Structure interview format, consisting of closed questions (Likert-scale), and open-ended questions	<ul style="list-style-type: none"> • The percentage of injections received to allow comparison with previous ARF/RHD studies. It was calculated by the number of received injections by the number recommended. 	<p>Medication adherence rate: Low adherence (n = 3 (6%): adequate adherence; n = 41 (82%): inadequate adherence; n = 6 (12%): data unavailable)</p> <p>Factors associated with adherence:</p> <ul style="list-style-type: none"> • Direct relationship - Reminder to attend the clinic - The flexible administration service model • Inverse relationship - Lack of understanding that injections were required - Feeling well and healthy - Transport unavailability - No medication supply at the clinic

Author, year	Study design	Purpose of the study	Study setting, Country	Study participants	Measurement	Definition of adherence	Study Finding
Grady et al., 2019	RCT (Feasibility, and pilot study)	To determine the feasibility and test a transition intervention for young adults who underwent heart transplantation as children and transferred to adult care	Six Children's Hospital, United State	<ul style="list-style-type: none"> Inclusion criteria: aged \geq 18 years; post heart transplantation at participating Children's Hospitals and ready to transfer care; able to speak, read, and write English; and physically able to participate Exclusion criteria: developmental delays; psychiatric hospitalization 	<ul style="list-style-type: none"> Medical record (medical records and resources utilization) Self-report questionnaires (HT Knowledge Questionnaire, Transition Readiness Assessment Questionnaire, Social Support Index, Patient level outcomes (Assessment of Problems with the HT Regimen)) 	<ul style="list-style-type: none"> Better self-reported adherence to the medical regimen (1 = hardly ever to 4 = all of time) Lower within-patient standard deviation (SD) of average tacrolimus blood levels at specific time points (primary endpoint) (i.e., < 2.5) More than 50% tacrolimus levels within the target range (determined 	<ul style="list-style-type: none"> Pain from injection Injection technique from less-experienced nurses Preference for an oral treatment due to injection pain Need for a greater explanation of when and how to get injections <p>Outcomes: Not reported</p> <p>Medication adherence rate:</p> <ul style="list-style-type: none"> Good adherence (average overall self-reported adherence) for both group Adequacy adherence referencing bioassays (average within-patient SD of tacrolimus levels < 2.5 in both groups) For the percentage of tacrolimus levels within the target range over time, the intervention group was higher than the control group at 3 (83% versus 51%) and 6 months. <p>Factors associated with adherence:</p> <ul style="list-style-type: none"> Not significant HT-related knowledge Satisfaction with support Self-advocacy

Author, year	Study design	Purpose of the study	Study setting, Country	Study participants	Measurement	Definition of adherence	Study Finding
				within previous 3 month (N = 88, Intervention: 43; Usual care: 45)		by HT cardiologists)	Outcomes: Not reported
Keval et al., 2021	Retrospective study	To determine secondary prophylaxis adherence rates in the Far North Queensland paediatric population and to identify factors contributing to suboptimal adherence	Far North Queensland, Australia	<ul style="list-style-type: none"> Inclusion criteria: Children with RHD aged 0 – 18 years residing in Far North Queensland who had an active status of disease and who received ≥ 5 injections. Exclusion criteria: who received < 5 injections in total. (N = 277) 	Not reported	<p>The proportion of injections given within investigated interval is $\geq 80\%$, which is the target recommendation for BPG delivery as per the Australian ARF/RHD guideline</p> <p>Factors associated with adherence:</p> <ul style="list-style-type: none"> • Direct relationship - individual or family unit - Increase the year of inclusion (interval 28 days) • Inverse relationship - Older age at the injection (interval 35 days) • Not significant - Gender - Ethnicity - Suburb - ARIA class - number of people per dwelling 	<p>Medication adherence rate:</p> <p>Low adherence (no children received $\geq 80\%$ of their injections within a 28-day interval (277 are non-adherence); 12% (32) of children received $\geq 80\%$ of their injections within 35 days.)</p>

Author, year	Study design	Purpose of the study	Study setting, Country	Study participants	Measurement	Definition of adherence	Study Finding
Killian, 2017	Predictive correlational study	To identify the pediatric recipient and family-related demographic, psychosocial, and condition-related characteristics predicting immunosuppressive medication adherence in a sample of children receiving either heart or lung transplants and their families.	United Network for Organ Sharing (UNOS; Department of Health and Human Service), United States	Pediatric patients (up to 18 years of age at the time of transplantation procedure) receiving pretransplant care and assessment, a cardiothoracic transplant, and the first-year post-transplant follow-up care at a large university-affiliated hospital and pediatric transplant center in the southeast United States. (N = 105)	<ul style="list-style-type: none"> Medical record UNOS data 	<ul style="list-style-type: none"> Any positive answer to a question during any follow-up period was considered evidence of post-transplant non-adherence Higher SD scores were indicative of greater non-adherence 	<ul style="list-style-type: none"> - Index of Relative Socio-economic Advantage and Disadvantage - Index of Education and Occupation <p>Outcomes: Not reported</p> <p>Medication adherence rate:</p> <ul style="list-style-type: none"> 34.1% of children were reported "evidence of non-compliance with immunosuppressive medication during the follow-up period that compromised the patient's recovery" by the physician The SD score for individual blood assay levels had a mean of 4.29 ± 1.79. The mean SD scores significantly differed ($t = 2.18$, $df = 77$, $p < 0.033$) between the groups of patients rated as adherent (mean = 3.99 ± 1.55) and the non-adherence (mean = 4.82 ± 1.70) by the physician. <p>Factors associated with adherence:</p> <ul style="list-style-type: none"> Direct relationship Age at the time of transplant Adequate financial support

Author , year	Study design	Purpose of the study	Study setting, Country	Study participants	Measurement	Definition of adherence	Study Finding
						<ul style="list-style-type: none"> - Private insurance - Parental education of a college degree or more - Two parents in the homes, including blended families - Hospitalized, in ICU - Other psychosocial stressors - Patients on life support at the time of being listed for a transplant • Inverse relationship - Increased age at the time of transplant - Experience of childhood maltreatment - Families with significant psychosocial problems, families' conflicts, and difficulty communicating in the family before transplantation influence non-adherence during the post-transplantation period 	
McAllister et al., 2006	Mixed-method study	To examine the differences in motivation between adolescents who are more adherent and	A heart transplant follow-up clinic in the southeastern United States,	<ul style="list-style-type: none"> • Inclusion criteria: Adolescents aged 12 to 18 years who had received a heart transplant, the 	<ul style="list-style-type: none"> • Quantitative: The Frazier Non-compliance Inventory, demographic information, and self-report 	<ul style="list-style-type: none"> • Criterion for adherence of greater than 75% • Evidence of non-adherence 	<p>Outcomes: Not reported</p> <p>Medication adherence rate: Overall adherence (4 participants reported adherence with a score more than or equal to 90%. However, one-fourth had evidence of non-</p>

Author , year	Study design	Purpose of the study	Study setting, Country	Study participants	Measurement	Definition of adherence	Study Finding
		those who are less adherent to their medication regimen following transplant surgery.		current treatment that included at least 3 medications (at least 1 immunosuppressive drug), and the ability to read, write, and speak English. ● Exclusion criteria: experiencing any physiologic or psychological distress on the day of the interview, and multiple transplantations (N = 4)	question regarding the amount of time participants adhere to their medication ● Qualitative: 19 open-ended questions	adherence "I still miss a couple of doses a week") Factors associated with adherence: ● Direct relationship - Family, friends, and community support - Increase expectation of self - Minimal lifestyle change - Expectations from the others - No negative side effects of medication ● Inverse relationship - Physiologic reasons: Felt healthy - Physiologic reasons: Side effects - Physiologic reasons: Inability to swallow oral medications - Psychological issue: Stress, depression, and control - Environmental issue: The desire to be part of a group - Environmental issue: The desire not to stand out for negative reasons - Environmental issue: Daily schedules - Environmental issue: Lower expectations from the others	

Author, year	Study design	Purpose of the study	Study setting, Country	Study participants	Measurement	Definition of adherence	Study Finding
Olivia et al., 2013	Retrospective study	To describe the incidence and risk factors for non-adherence and outcomes after non-adherence in a large United States multicenter cohort of children who have undergone HT.	Organ Procurement Transplant Network (OPTN) data provided courtesy of the United States Network for Organ Sharing (UNOS; Department of Health and Human Service), United States	All pediatric aged < 18 years who underwent orthotopic heart transplantation in the United States (N = 2070)	<ul style="list-style-type: none"> • OPTN data 	<ul style="list-style-type: none"> • Non-adherence is defined as “evidence of non-compliance with immunosuppression on medication that compromised the patient’s recovery”. • A patient was defined to be non-adherence when first reported being so. 	<ul style="list-style-type: none"> - Identity issue: Expectations of self - Identity issue: Responsibility - Identity issue: Image change - Dependence issues such as blame, safety, and reliance <p>Outcomes: Not reported</p> <p>Medication adherence rate:</p> <ul style="list-style-type: none"> Non-adherence reported in 186(9%), and non-adherence was not reported in 1884 (91%) <p>Factors associated with adherence:</p> <ul style="list-style-type: none"> • Inverse relationship - Older age at transplant - cardiomyopathy diagnosis - Race (black race) - Medical insurance - mild renal dysfunction - Ventilator or VAD support at the transplant - time on the wait list of between 2 and 3 months <p>Outcomes:</p> <ul style="list-style-type: none"> • 26% risk of mortality after the first report of non-adherence at 1 year and 33% at 2 years • Graft loss events treated with re-transplantation

Author, year	Study design	Purpose of the study	Study setting, Country	Study participants	Measurement	Definition of adherence	Study Finding
Wolfe et al., 2020	Retrospective study	To examine the hypothesis that the overall sample would show mild-to-moderate impairments in intelligence and language and that this pattern would extend across the additional neuropsychological domains, with children with premorbid cardiomyopathy scoring relatively better compared to those with	Children's Hospital Colorado, United States	<ul style="list-style-type: none"> ● Inclusion criteria: ages 4 to 18 years at the time of the neuropsychological evaluation, the neuropsychological evaluation took place after the heart transplantation, and patients received care through the Children's Hospital Colorado around the time of the neuropsychological evaluation. ● Exclusion criteria: primary language was not 	<ul style="list-style-type: none"> ● Electronic medical record ● Neuropsychological testing <ul style="list-style-type: none"> - IQ: the Wechsler Intelligence Scale for Children (WISC), the Wechsler Adult Intelligence Scale (WAIS), the Wechsler Preschool and Primary Scales of Intelligence (WPPSI) - Working memory and processing speed: IQ tests - Word reading and numerical operations: the Wechsler 	<ul style="list-style-type: none"> ● The medication target range for each individual patient was identified from the clinic notes and compared with the actual laboratory values ● Laboratory results were in the range: this was coded as "adherence (1)" ● If the laboratory results were out of range in either direction, this was coded "non-adherence (0)" 	<ul style="list-style-type: none"> ● 27% risk of graft loss at 1 year and 35% at 2 years after the first report of non-adherence ● Cause of death in 16 children who died after their episode of non-adherence <p>Medication adherence rate: Not reported</p> <p>Factors associated with adherence:</p> <ul style="list-style-type: none"> ● Direct relationship - Parent-reported attention concerns in the children ● Not significant - Medical history - Demographic characteristics - Neuropsychological test scores <p>Outcomes: Not reported</p>

Author , year	Study design	Purpose of the study	Study setting, Country	Study participants	Measurement	Definition of adherence	Study Finding
		<p>premorbid CHD.</p> <p>To examine the hypothesis that medical variables reflect a more complicated course, as well as poorer adherence to immunosuppre- ssant medication, would be related to poorer neuropsycholo- gical functioning.</p>		<p>English, have medical conditions affecting the central nervous system unrelated to heart failure/transplant ation (N = 27)</p>	<p>Individual Achievement Test (WIAT) - Verbal memory: the Long Delay Free Recall z-score from the California Verbal Learning Test (CVLT) - Patient report of executive functioning; the Behavior Rating Inventory of Executive Function (BRIEF) - Parent report of attention- deficit/hyperactivit y disorder (ADHD) symptoms: the National Institute of Child Health Questionnaire (NICHQ) Vanderbilt Rating Scale - Patient report of adaptive functioning; the</p>		

Author , year	Study design	Purpose of the study	Study setting, Country	Study participants	Measurement	Definition of adherence	Study Finding
					Adaptive Behavior Assessment System (ABAS)		

Table 2, The Characteristics and result of an individual source of evidence

3. Synthesis of results

The synthesis of results was conducted according to the review's objective as follows,

- 3.1 To identify medication adherence rates in children and young adults with cardiovascular disease
- 3.2 To identify medication adherence factors in children and young adults with cardiovascular disease
- 3.3 To explore the outcome of medication adherence and non-adherence in children and young adults with cardiovascular disease.

3.1 Medication adherence rate

In this section, it will be synthesized into two groups, including injection adherence, and oral medication adherence.

Injection adherence studies were mostly conducted on rheumatic heart disease patients. Out of 1300 RHD participants, 259 (20%) participants were adherence. 568 (44%) participants were non-adherence by defined adherence with the proportion of days coverage ($PDC \geq 80\%$). 473 participants were not received secondary antibiotic prophylaxis (SAP) of benzathine penicillin G (BPG), and unavailable data (Adem et al., 2022; Kevat et al., 2021; Beaton et al., 2017; Culliford-Semmens et al., 2017; Engelman et al., 2017; Engelman et al., 2016). For defined adherence with the proportion of days coverage ($PDC > 75\%$), Balbaa et al. found that 19 participants (65.5 %) adhered to injection (Balbaa et al., 2015). Moreover, Alkan et al found that 31 (72%) children with RHD adhered to injection medication (Alkan et al., 2022).

For medication adherence rate of oral medication, two studies out of four not reported the number of participants who were adherent. Gardy et al (2019) found that 88 participants had good adherence by self-report and adequate adherence by blood assays (Grady et al., 2019). In contrast, Killian (2017) found that 34.1% of participants were non-adherence by physician's assessment. For blood assays, the mean SD of individual blood assays was 4.29 ± 1.79 (Killian, 2017). Two studies reported the number of adherence participants. Of 2070

participants, 1884 (91%) participants adhered to an immunosuppressive medication (Olivia et al., 2013). Regarding Olivia et al.'s study, they did not report that adherence status was assessed by physicians or reported by patients. Moreover, McAllister et al. conducted a mixed-method study and used self-report to assess the patient's adherence. They found that three out of four heart transplantation patients adhered to the medication regimen (McAllister et al., 2006).

3.2 Medication adherence factors

Factors associated with adherence were analyzed and mapped based on the COM-B model of behavior change. In this review, factors were separately analyzed into two groups, including factors associated with injection adherence, and factors associated with oral medication adherence.

3.2.1 Factors associated with injection adherence

The factors were analyzed following the COM-B model subcomponents, as shown in Table 3. Moreover, direct relationships, inverse relationships, and inconsistent relationships were mapped following the COM-B model for easy understanding, as illustrated in Figure 2.

Psychological capability

This subcomponent explored the psychological capability of participants to adhere to injection medication. One study reported factors associated with injection adherence in rheumatic heart disease patients. Understanding the disease was a significant factor influencing injection adherence. A study conducted among children with RHD in Egypt reported that 68.4% of children with RHD, who were adherence, were knowledgeable about RHD compared with non-adherence ($p = 0.021$) (Balbaa et al., 2015). For the non-adherence factor, Alkaan et al (2022) found that “forgetting to take the medication” was significantly associated

with injection non-adherence among children with RHD in Turkey ($p = 0.009$) (Alkan et al., 2022).

For not significant factors, Alkan et al. found that attention deficit hyperactivity was not a significant factor that could influence patients to be non-adherence in rheumatic heart disease patients ($p = 0.698$) (Alkan et al., 2022).

Physical capability

This subcomponent was the physical capability of participants to adhere to oral medication. In this subcomponent, age was an inconsistent relationship with adherence. In 2021, Kevat et al. found that older age at the injection was a significant factor affecting children with RHD's adherence to receiving injection medication. He found that older age at the injection was a significant factor associated with increased risk for interval days of delivery of injection ≤ 35 days overdue ($OR = 1.46$, 95% CI = $1.24 - 1.71$) (Kevat et al., 2021). In contrast, Alkan et al. (2022) found that age was not a significant factor affecting injection adherence in children with RHD ($p = 0.183$).

Moreover, two studies found three factors that were not affecting injection adherence in children with RHD. For characteristics of patients, gender is not a significant factor associated with injection adherence ($p = 0.399$) in children with RHD (Alkan et al., 2022; Kevat et al., 2021). In addition, disease type (according to major findings) and severity of rheumatic heart disease (degree of carditis) were not significant factors associated with injection adherence in Turkestan children ($p = 0.886$, $p = 0.369$) (Alkan et al., 2022).

Reflective motivation

This subcomponent was the motivation which involves

conscious thought processes. According to included studies, there were four factors, including belief about aversion to receiving treatment by injection, belief about the necessity of treatment, belief about future adverse events of treatment, and perception of health (feeling well and healthy). Three studies reported the effect of belief about treatment on injection adherence (Alkan et al., 2022; Engelman et al., 2017; Balbaa et al., 2015). We found three kinds of belief about treatment, including general aversion, necessity, and adverse events.

For belief about aversion to receiving treatment by injection, one study reflected the relationship between no fear of syringes and injection adherence in children with RHD. Alkan et al. found that 83.9% of the adherence group had no fear of syringes. That means no fear of syringes affecting injection adherence in children with RHD ($p = 0.047$) (Alkan et al., 2022).

Belief about the necessity of treatment was an inconsistent factor affecting injection adherence. In 2015, Balbaa et al. found that 79% of children with RHD, who were adherence, have a direct relationship with awareness of the consequences of missing prophylaxis doses ($p = 0.005$). That reflected the patient's belief in the necessity of treatment. On the contrary, Balbaa et al. conducted a study among children with rheumatic heart disease to evaluate the barriers to secondary prophylaxis use in Aswan, Egypt by developing an instrument using Fishbein's integrative model of behavior. This model assumes that behavior would potentially occur if one has the ability, a strong intention, and no environmental constraints. They found that 90% of non-adherence children with RHD consciously choose to miss injection appointments by themselves ($p = 0.005$) which was one of the factors under the domain of intention (Balbaa et al., 2015). That

means they did not have the intention to receive the injection and it was not necessary. Moreover, Engelman et al. (2017) found that 42% of participants reported their reasons for missing injection were “did not know need” (Engelman et al., 2017). The aforementioned, belief in the necessity of treatment can influence adherence in positive and negative ways. It depended on how much they believed it necessary.

For belief about future adverse events of treatment, there were no significant factors affecting injection adherence. Alkan et al found that fear of adverse events and fear of addiction were not significant factors associated with injection adherence in children with RHD ($p = 0.460$, $p = 0.123$). In the non-adherence group, only 5 (41.7%) and 3 (25%) of participants reported fear of adverse events and fear of addiction, respectively (Alkan et al., 2022). Even though he did not report the number of adverse events, we can imply that most of the participants had no experience with adverse events or that adverse events did not affect their health. Moreover, benzathine penicillin G was not an addictive drug. So, that’s why most of the participants did not report a fear of addiction.

The other factor was the perception of health. A study conducted among children with RHD in Fiji reported that 46% of participants documented feeling well and healthy to be the reason for missing injections (Engelman et al., 2017). That means the perception of health on a positive side would inversely influence injection medication.

Automatic motivation

This subcomponent was the motivation which involves habitual, instinctive, drive-related, and affective processes (e.g.,

desires and habits). Unfortunately, there were no significant factors associated with injection adherence in included studies. Even though Alkan et al. studied the relationship between automatic motivation factors such as lifestyle, conduct problems, emotional problems, and social behavior with injection adherence, there were no statistical significance factors among all of them ($p = 1.000$, $p = 0.679$, $p = 0.081$, $p = 0.547$).

Physical opportunity

This subcomponent was an opportunity that involves inanimate parts of the environment system and time. In this subcomponent, one study showed a significant factor directly affecting injection adherence. In 2021, Kevat et al. found that increasing year of inclusion was a significant factor directly reducing risk of the interval ≤ 28 days of delivery of injection overdue (OR = 0.940, 95% CI = 0.896-0.987) (Kevat et al., 2021).

For factors inversely associated with injection adherence, two studies reported four factors associated with injection non-adherence (Engelman et al., 2017, Engelman et al., 2016). Engelman et al. (2016) found that time since diagnosis ≥ 1.5 years was inversely associated with injection adherence in children with RHD, who was diagnosed with echocardiography (OR = 0.38, 95% CI = 0.17-0.83, $P = 0.02$). The second factor is transport unavailable. One study conducted among children with RHD in Fiji reported 46% of participants mentioned that transport unavailability was a reason for missing injections. Moreover, this study found that 42% of participants reported medication unavailability was also a reason for missing injection medication (Engelman et al., 2017).

The physical characteristic of injection medication was associated with injection non-adherence. Engelman et al. (2017) found that 60% of participants had experienced very pain during the first-time injections. Moreover, 28% of participants reported pain from injections caused them to miss injections. In addition, some participants preferred to take an oral treatment over an injection due to pain and concerned regarding an injection technique from less-experienced nurses (Engelman et al., 2017). Differences between the above and “belief about aversion to receiving treatment by injection” in the “Reflective motivation” are somewhat different. Aversion of medicine means a dislike of taking medicines that would minimize drug taking, stopping prescriptions, etc. (Britten et al., 2004). For the physical characteristic of medicine, it means the taste, smell, size, route, etc. of medicine affecting taking medicine. So, that’s why the aversion to receiving injections and the physical characteristic of injection medication are different.

Factors, inconsistently associated with injection adherence, were reported in 4 studies. The area of living was studied in three studies. Engelman et al. (2016) found that urban residence was a significant factor affecting injection adherence in children with RHD (OR = 3.37, 95% CI = 1.54-7.37, $p = 0.002$) (Engelman et al., 2016). In contrast, Alkan et al. (2022) found that area of living was no statistical difference between the adherence and non-adherence groups (Alkan et al, 2022). Similarly, one study in Australia found that living in a suburb was no significant factor affecting longer interval of delivery of injection in children with RHD (injection interval > 28 days: $p = \text{“redundant”}$, injection interval > 35 days: $p = 0.289$) (Kevat et al., 2021).

Ten factors were reported as not significant factors

associated with injection adherence in children with RHD. Factors were Hospital accessibility (Alkan et al., 2022; Kevat et al., 2021), educational status of parents, lack of health insurance, medication accessibility, long-term treatment, adequate support from the physician (Alkan et al., 2022), screening activity type (Engelman et al., 2016), a reminder to attend the clinic, the flexible administration service model (Engelman et al., 2017), and economic and social condition in the community (Kevat et al., 2021).

Social opportunity

This subcomponent consists of external factors that involve other people and the organization that influences the performance of the behavior. Individual or family unit was a significant factor affecting injection adherence in children with RHD (Kevat et al., 2021). Another factor was ethnicity. Engelman et al. found that the non-iTaukei population (Fijian-Indian), who are not a nation and ethnic group in Fiji, ethnicity was associated with adequate injection adherence among children with RHD in Fiji (OR = 2.57, 95% CI = 1.04-6.33, $p = 0.04$) (Engelman et al., 2016). In contrast, Kevat et al. found that Aboriginal and/or Torres Strait Island background, two indigenous in Australia, was not a significant factor affecting longer intervals > 28 days and > 35 days of delivery of injection among children with RHD in Australia (OR = 0.678, 95% CI = 0.678-1.53, $p = 0.930$; OR = 1.64, 95% CI = 0.967-2.78, $p = 0.0664$) (Kevat et al., 2021). The differentiation between the two studies is the Aboriginal and/or Torres Strait Island backgrounds are small indigenous but the non-iTaukei is neither.

In this subcomponent, 11 not significant factors were reported in two studies. Factors were problem-solving in the

family, communication in the family, role in the family, emotional responsiveness in family, attention in the family, behavior control in the family, general function in family, peer problems (Alkan et al., 2022), number of people per dwelling, educational and occupational level of community, and economic and social condition in the community included (Kevat et al., 2021).

Injection Adherence			
COM-B subcomponents	Relationship	Factors	Sources
Capability			
Psychological capability	+	Understanding of the disease	Balbaa et al., 2015
	-	Forgetting to get a prescription and/or take the drug when the time	Alkan et al., 2022
	±	None	
	NS	Attention deficit hyperactivity	Alkan et al., 2022
Physical capability	+	None	
	-	None	
	±	Age	Alkan et al., 2022 (NS); Kevat et al., 2021 (-)
	NS	Gender	Alkan et al., 2022; Kevat et al., 2021
		Disease type	Alkan et al., 2022
		Severity	Alkan et al., 2022
Motivation			
Reflective motivation	+	Belief about aversion to receiving treatment by injection (No fear of syringes)	Alkan et al., 2022
	-	Feeling well and healthy	Engelman et al., 2017
	±	Belief about the necessity of treatment (Awareness of the consequences of missing prophylaxis doses; Consciously choosing to miss an injection appointment; Lack of understanding that injections were required)	Balbaa et al., 2015 (+), (-); Engelman et al., 2017 (-)
	NS	Belief about future adverse events of treatment (Fear of developing adverse effects; fear of addiction)	Alkan et al., 2022

Injection Adherence			
COM-B subcomponents	Relationship	Factors	Sources
Automatic motivation	+	None	
	-	None	
	±	None	
	NS	Conduct problems	Alkan et al., 2022
		Emotional problems	Alkan et al., 2022
		lifestyle	Alkan et al., 2022
		Social behaviors	Alkan et al., 2022
Opportunity			
Physical opportunity	+	Increase the year of inclusion (interval 28 days)	Kevat et al., 2021
	-	Time since diagnosis ≥ 1.5 years	Engelman et al., 2016
		Transport unavailability	Engelman et al., 2017
		Medication unavailability	Engelman et al., 2017
		The physical characteristic of injection medication (Pain from injection, Preference for an oral treatment due to injection pain, Injection technique from less-experienced nurses)	Engelman et al., 2017
	±	Living in rural areas and cities	Alkan et al., 2022 (NS); Engelman et al., 2016 (Urban, +); Kevat et al., 2021 (Suburb, NS)
		Treatment clarification (Need for a greater explanation of when and how to get injections; Enough information)	Engelman et al., 2017 (-); Alkan et al., 2022 (NS)
	NS	Hospital accessibility	Alkan et al., 2022; Kevat et al., 2021
		Educational status of parents	Alkan et al., 2022
		Lack of health insurance	Alkan et al., 2022
		Medication accessibility	Alkan et al., 2022
		Long-term treatment	Alkan et al., 2022
		Adequate support from the physician	Alkan et al., 2022
		screening activity type	Engelman et al., 2016
		Reminder to attend the clinic	Engelman et al., 2017

Injection Adherence			
COM-B subcomponents	Relationship	Factors	Sources
		The flexible administration service model	Engelman et al., 2017
		Economic and social condition in the community (Index of Relative Socio-economic Advantage and Disadvantage)	Kevat et al., 2021
Social opportunity	+	individual or family unit	Kevat et al., 2021
	-	None	
	±	Ethnicity	Engelman et al., 2016 (+); Kevat et al., 2021 (NS)
	NS	Problem-solving in the family	Alkan et al., 2022
		Communication in the family	Alkan et al., 2022
		Role in the family	Alkan et al., 2022
		Emotional responsiveness in family	Alkan et al., 2022
		Attention in the family	Alkan et al., 2022
		Behavior control in the family	Alkan et al., 2022
		General function in the family	Alkan et al., 2022
		Peer problem	Alkan et al., 2022
		number of people per dwelling	Kevat et al., 2021
		Educational and Occupational level of community (Index of Education and Occupation)	Kevat et al., 2021
		Economic and social condition in the community (Index of Relative Socio-economic Advantage and Disadvantage)	Kevat et al., 2021

Table 3, Described factors associated with injection adherence.

*Note: “+”, direct relationship; “-”, inverse relationship; “±”, inconsistent relationship;

“NS”, not significant factors

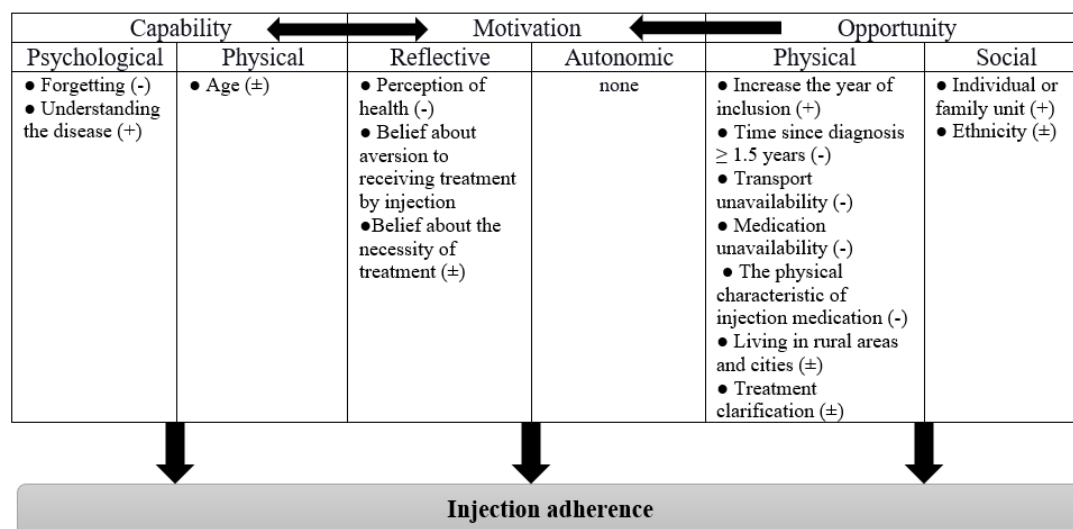


Figure 3, Illustrated a framework of factors associated with injection adherence by using the COM-B model of behavior change. * Note: “+”, direct relationship; “-”, inverse relationship; “±”, inconsistent relationship

3.2.2 Factors associated with oral medication adherence.

The factors were analyzed following the COM-B model subcomponents, as shown in Table 4. Moreover, direct relationships, inverse relationships, and inconsistent relationships were mapped following the COM-B model for easy understanding, as illustrated in Figure 3.

Psychological capability

This subcomponent was a capability that involves a person’s mental functioning that influences participants to adhere to oral medication. Three studies reported four factors related to this subcomponent. Killian (2017) found that children with heart transplantation, who experienced maltreatment in their childhood before transplantation, was associated with a 78% decrease in potential adherence later (Exp β = 0.217, p = 0.042) (Killian, 2017). The other factors were not associated with oral medication adherence. Factors were HT-related knowledge, Self-advocacy (Grady et al., 2019), and Neuropsychological test scores (Wolfe et

al., 2020).

Physical capability

This subcomponent was the physical capability of participants to adhere to oral medication. There was one significant factor directly affecting oral medication adherence. The severity of the disease was reported as a significant factor associated with oral medication adherence. Killian et al. found that the patient's status before transplantation was significantly related to oral medication adherence. They found that children who were hospitalized and admitted to intensive care during place on the waiting list for heart transplantation showed higher adherence. It was approximately more than 3.3 times more to likely be adherent by a physician assessment (Exp $\beta = 3.31$, $p = 0.04$) and had an SD score of blood assays 4.73 lower (Exp $\beta = -4.73$, $p = 0.014$) (Killian, 2017).

Three factors were reported as having an inverse relationship with oral medication non-adherence in two studies, including Cardiomyopathy diagnosis, ventilator or VAD support at the transplant, and normal renal dysfunction. Olivia et al. (2013) reported children who were diagnosed with cardiomyopathy before heart transplantation had a significant association with oral medication non-adherence ($p = 0.001$). Moreover, they reported that mild-moderate renal function had a significant association with oral medication non-adherence in children with heart transplantation ($p = 0.02$). In addition, Olivia et al. found that participants, who received ventricular assist devices (VAD) that supported their hemodynamics during transplantation, had a significant association with oral medication non-adherence after transplantation ($p = < 0.001$). Besides, Olivia also performed multivariable analysis and found that ventilator or VAD support at

transplantation was a predictor of oral medication non-adherence (HR = 1.8, 95% CI = 1.2-2.9, $p = 0.007$; HR = 1.5, 95% CI = 1.0-2.3, $p = 0.04$, respectively) (Olivia et al., 2013).

Factors, inconsistently associated with oral medication adherence, were age at the time of transplant and side effects. Killian found that age at the time of transplant was an associated factor with oral medication adherence (Exp $\beta = 0.918$, $p = 0.039$). Moreover, he performed multivariate regression and found that the age of children at the time of transplantation could predict oral medication adherence during post-transplantation by physician assessment (Exp $\beta = 0.89$, $p = 0.034$) and predict a patient SD score of blood assays (Exp $\beta = 0.074$, $p = 0.020$). Moreover, an additional year of age was associated with the raising of SD scores of blood assays, which means greater non-adherence (greater non-adherence) (Killian, 2017). Finally, two factors were reported as not significant factors, including medical history and Demographic characteristics (Wolfe et al., 2020).

For side effects, McAllister et al. (2006) found that non-adherence in children with heart transplantation concerned regarding side effects because she confronted with side effects at the first time of taking medication. They were negative cosmetic and physiologic changes as a result of the medication.

“The side effects of acne, hair growth, and stomach aches were really bad at first” (McAllister et al., 2006).

On the contrary adherent children, they had not experienced any negative side effects of medication.

Reflective motivation

This subcomponent was the motivation which involves

conscious thought processes. In this scoping review, no study reported a factor that was associated with oral medication adherence. Two studies reported three factors that were associated with oral medication non-adherence (Killian, 2017; McAllister et al., 2006). One study reported two factors had an inconsistent relationship with oral medication adherence (McAllister et al., 2006).

McAllister et al. performed the mixed-method study and found that non-adherence children with heart transplantation stated that their positive perception of health (feeling well and healthy) affected their oral medication non-adherence.

One participant said “The first time I quit [taking medication] was when I went back to school and was feeling healthy again” (McAllister et al., 2006)

McAllister et al. mentioned that “she felt healthy” was a physiologic reason for missing oral medication in non-adherence children (McAllister et al., 2006).

In addition, this participant also stated that a major psychological barrier to taking medication was an inability to swallow oral medication.

One participant said “I couldn’t swallow pills at all before my transplantation; it used to take an hour for me to take my pills because I would have to take them one at time.” (McAllister et al., 2006)

Referring to her sentence, it was not only reflecting the problematic physical characteristics of oral medication but also reflecting general aversion to oral medication.

For inconsistent relationship factors, McAllister et al.

reported expectations of self was inconsistently associated with oral medication adherence among children with heart transplantation. McAllister et al. mentioned that identity issues potentially affected adolescents referring to their developmental stage and included the expectation of self.

One child with heart transplantation said that “It has changed my expectations in myself... I used to want to be a doctor so bad and I used to stress out every little grade, now, it’s like what is the point if by the time I get out of medical school I only have 10 years to live?” (McAllister et al., 2006).

In contrast, children with heart transplantation, who adhered to medication, stated that adherence was motivated by increasing their own expectations.

“It [transplant] made me grow up” and “I plan to start college in the spring” (McAllister et al., 2006).

As above, the expectation of self would have an inconsistent relationship with medication adherence. It would be depended on their expectations or belief in themselves.

Automatic motivation

This subcomponent was the motivation which involves habitual, instinctive, drive-related, and affective processes (e.g., desires and habits). Referring to included studies, McAllister et al. reported 6 factors, including Stress, depression, and control; a sense of belonging (the desire to be part of a group, and the desire not to stand out for negative reasons); responsibility; dependence issues (blame, safety, and reliance); image change; and lifestyle change (McAllister et al., 2006).

McAllister et al. found that non-adherence children mentioned the psychological issue that influenced non-adherence.

“When I get depressed or stressed about something I would take my anger out on my meds because it is something I can control and no one else really knows”
(McAllister et al., 2006).

Her quote would be implied that stress was an affective process and influenced children’s behavior. In this case, children coped with his mental issue by controlling his medication taking with not taking medication (non-adherence).

Besides, the desire of a participant was associated with medication non-adherence. McAllister et al. reported two types of desires, including the desire to be part of a group and not to stand out for negative reasons.

Non-adherence children said that “Sometimes I don’t want to bother people to go and take my pills...I don’t like being different, leaving the group to go home and take my meds.”
(McAllister et al., 2006).

Her quote implied to desire to be part of a group that was influenced by the environment. In addition, she also did not want to stand out in public. This desire was influenced by the environment as well.

“I have to take them [meds] at lunch in the cafeteria and some people might ask or look at me funny” (McAllister et al., 2006).

This desire would be interpreted that they want to be part of their environment. Hence, I would condense both factors to be a “sense of belonging”.

The other factor was identity issues. In McAllister et al.'s study, they found two types of identity issues, including responsibility, and image change.

Non-adherence children said that "I am completely responsible for my meds...now that I am in college people don't really know about my meds. I could not take them for a week and no one would know...That is kind of scary" (McAllister et al., 2006).

Her quote implied that even though she had a responsibility before, it would be decreased by environmental change.

For image change, the non-adherence child stated that she felt changes in self-image and could not control it.

"I used to be known for my grades and my character and then it was 'the girl with the transplant'" (McAllister et al., 2006).

This quote illustrated how the environment affects self-image. So, they would be denied taking medication because of reducing self-image change.

The last factor influencing non-adherence was the dependence issue. McAllister et al. found that children had a dependence on their doctors and used it be a reason for non-adherence to a medication regimen.

"I am kind of dependent on my doctor; like right now I really miss them and sometimes I think I might make up symptoms just to come home and see them. It is so easy to live your life as a sick person because no one really expects anything from you." (McAllister et al., 2006).

The dependence issue was supported by two quotes from children with non-adherence.

“I kind of blame things on the medicine” and “Sometimes when I get stressed out at school, I just want to fall back into my little safety net” (McAllister et al., 2006).

As above, dependence issues could influence medication adherence in a negative way if children could not independently live, cope, and manage everything by themselves.

For lifestyle, it was an inconsistent factor associated with medication adherence. McAllister et al. compared adherence and non-adherence in children with heart transplantation. They found that adherence children stated that their lifestyle was minimally changed.

“At first when I started taking them it was kind of awkward, now I just take them in Wal-Mart, or wherever” (McAllister et al., 2006).

Moreover, his minimal lifestyle change was supported by his statement that.

“I still do all the things I used to do: hunt and ride 4-wheelers,” (McAllister et al., 2006).

In contrast, the children with non-adherence experienced dramatic lifestyle changes (McAllister et al., 2006). Hence, lifestyle change was influenced by transplantation and was associated with medication adherence, systematically.

Physical opportunity

This subcomponent was an opportunity that involves inanimate parts of the environment system and time. One study

reported one factor influencing medication adherence (Killian, 2017). Two studies reported four factors inversely influencing medication non-adherence (Olivia et al., 2013; McAllister et al., 2006). However, no study reported factors that inconsistent relationship with medication adherence. Killian found that Adequate financial resources were an associated factor with medication adherence among children with heart transplantation. Killian stated that the family's socioeconomic status was significantly associated with the physician's assessment of adherence in children to the immunosuppressant medication. Killian mentioned that if their families had adequate financial resources, their children would be more than 3.5 times to be rated as adherent (Exp β = 3.54, p = 0.010). Moreover, if their transplant cost was supported by private insurance, adherence rates were over 6 times (Exp β = 6.04, p = 0.007) (Killian, 2017). Having private insurance not only referred to sufficient resources for medical costs but also the cost of living as well.

For an inverse relationship, four factors were reported within two studies. Factors were daily schedule, the physical characteristic of oral medication, Medicaid insurance, and Time on the wait list of between 2 and 3 months (Olivia et al., 2013; McAllister et al., 2006). McAllister et al. found that a non-adherence child was concerned about her daily schedule.

"I feel like I have to revolve my day around when I am going to take meds" (McAllister et al., 2006).

For the physical characteristic of oral medication, the non-adherence child also mentioned that inability to swallow oral medicine was a major physiologic barrier to taking medicines. Even though this factor was mentioned before in the previous subcomponent because it was relevant to the general aversion to

oral medication, it was also implied to physical characteristics of oral medication as well such as taste, size, shape, route, etc.

Non-adherence child said that “I couldn’t swallow pills at all before my transplantation... It used to take an hour for me to take pills because I would have to take them one at a time.” (McAllister et al., 2006).

Regarding Medicaid insurance, it was separated from private insurance because it was large and federal public health insurance that was different from private insurance. A study conducted among children with heart transplantation in the USA reported that 60% of non-adherence children were supported their medical costs by Medicaid insurance which means it was associated with medication non-adherence in children with heart transplantation (HR = 2, 95% CI = 1.5-2.7, $p < 0.001$) (Olivia et al., 2013).

Generally, children, who needed to receive heart transplantation, had to register their names on the waiting list and wait until their turn. Olivia et al. reported that time on the wait list on an associated factor with medication non-adherence in children with heart transplantation (HR = 1.6, 95% CI = 1.1-2.5, $p = 0.02$) (Olivia et al., 2013). That means the prolonged waiting on the list for heart transplantation influenced children to be non-adherence.

Social opportunity

In this subcomponent, the opportunity involved other people and organizations (e.g., culture and social norms). Four studies reported five factors that were associated with medication adherence among children with heart transplantation. For inverse relationships, four factors were reported in two studies. Besides, one study reported one factor was associated with medication

adherence. Even though ten factors were reported in five studies, seven of them were factors regarding family characteristics, and environment. Moreover, one study reported evidence that social support was associated with medication adherence among children with heart disease. Hence, this subcomponent was described from the family characteristics to the other factors that involved other persons.

Characteristics of the family were significantly associated with medication adherence among children with heart transplantation. Killian reported that two parents in the home (including blended families) and high parental education (more than a college degree) were more probably to have their children rated adherent with medication adherence in children with heart transplantation ($\text{Exp } \beta = 5.04, p = 0.007$; $\text{Exp } \beta = 3.36, p = 0.012$). In addition, Killian found that both factors could predict the possibility of having children with medication adherence after transplantation (parental education: $\text{Exp } \beta = 4.36, p = 0.036$; two-parent homes: $\text{Exp } \beta = 3.24, p = 0.042$) (Killian, 2017).

For family environment, it was reported in two studies. However, this factor could influence medication adherence in heterogenic results. For direct relationships, Killian (2017) found that children who had parental other psychosocial stress were more likely to have children rated as adherent ($\text{Exp } \beta = 0.385, p = 0.042$). Moreover, it could predict the likelihood of having children with medication adherence after transplantation ($\text{Exp } \beta = 0.31, p = 0.045$) (Killian, 2017). In his study, he defined “other psychosocial stressors” as the psychosocial stressors at the family level such as impending divorce, problems with housing, serious financial concerns, the recent death of a family member, etc. However, financial resources were described in the previous

subcomponent. For impending divorce, the author infers that it was referred to the family conflicts. So, it will be described in the inverse relationship section. Thus, in this factor, other psychosocial stressors were implied to be problems with housing, the death of a family member, and others.

Family environment factors, which were inversely associated with medication adherence, were family conflicts, and difficulties in communication in families. Killian found that the history of family conflicts before transplantation was more having the probability of having children rated as non-adherence during the post-transplantation (Exp $\beta = 2.81$, $p = 0.046$). Moreover, if a family had a difficulty in communication, it was more likely to have children rated as adherence after transplantation (Exp $\beta = 6.73$, $p = 0.008$) (Killian, 2017).

As above, family conflicts and difficulties in communication among family members would decrease support from family members. In contrast, Grady et al. reported that children with heart transplantation, who adhered to their medication, had satisfaction with social support (Grady et al., 2019). Similarly, a study conducted among children with heart transplantation in the USA reported that support from family, friends, and the community was a major predictor of adherence.

“I have friends that call and remind me constantly...I come from a small town where everyone is more protective of me” (McAllister et al., 2006)

Moreover, Wolfe et al. (2019) found that attention concerns in children from the parent was related to better adherence to taking immunosuppressive medication among children with heart transplantation in the USA (Fisher’s exact test,

$p = 0.02$) (Wolfe et al., 2019).

Even though social support was a significant factor related to medication adherence in children with a heart transplant, expectations from others could influence medication adherence in heterogenic ways. McAllister et al. found that lower expectations from school people were related to medication non-adherence.

Non-adherence children said that “My teacher didn’t expect as much from me and would give me extra time on assignment...My volleyball coach wouldn’t push me as hard even though she could have and I wish she would have” (McAllister et al., 2006).

In contrast, children, who adhered to medication, stated that increased others’ expectations motivated his adherence.

“I work in construction...Yesterday, I worked 20 hours...I still do all things I used to do: hunting and ride 4-wheelers” (McAllister et al., 2006).

Referring to the previous statement regarding others’ expectations, the expectations from others could be binary results. The level of expectations must be considered for every people around children with heart transplantation. It should be sufficient for children and not over/or lesser for them. Hence, “compromising” was an important skill for people surrounding children with heart transplantation.

The last factor was race. Olivia et al. conducted a study on children with heart transplantation in the USA and performed multivariable analysis for predicting factors for non-adherence. They found that the black race was associated with non-adherence among children with heart transplantation in comparison with the

white race (HR 2.3, 95% CI = 1.7-3.3) (Olivia et al., 2013). She discussed that medication non-adherence is possibly related to differences in socioeconomic factors such as limited family resources, language barriers, accessibility, etc.

Oral medication Adherence			
COM-B subcomponents	Relationship	Factors	Sources
Capability			
Psychological capability	+	None	
	-	Experience of childhood maltreatment	Killian, 2017
	±	None	
	NS	HT-related knowledge	Grady et al., 2019
		Neuropsychological test scores	Wolfe et al., 2020
		Self-advocacy	Grady et al., 2019
Physical capability	+	The severity of disease (Hospitalized, in ICU, Patients on life support at the time of being listed for a transplant)	Killian, 2017
	-	Cardiomyopathy diagnosis	Olivia et al., 2013
		Ventilator or VAD support at the transplant	Olivia et al., 2013
		Mild-moderate renal function	Olivia et al., 2013
	±	Age at the time of transplant	Killian, 2017; Olivia et al., 2013
		Side effects	McAllister et al., 2006
	NS	Medical history	Wolfe et al., 2020
		Demographic characteristics	Wolfe et al., 2020
Motivation			
Reflective motivation	+	None	
	-	Perception of health (Feeling healthy)	McAllister et al., 2006
		A general aversion to oral medication (Inability to swallow oral medications)	McAllister et al., 2006
	±	Expectations of self	McAllister et al., 2006
	NS	None	
Automatic motivation	+	None	
	-	Stress, depression, and control	McAllister et al., 2006

Oral medication Adherence			
COM-B subcomponents	Relationship	Factors	Sources
		Sense of belonging (the desire to be part of a group, and the desire not to stand out for negative reasons)	McAllister et al., 2006
		Responsibility	McAllister et al., 2006
		Dependence (blame, safety, and reliance)	McAllister et al., 2006
		Self-image change	McAllister et al., 2006
	±	Lifestyle change	McAllister et al., 2006
	NS	None	
Opportunity			
Physical opportunity	+	Adequate financial resources	Killian, 2017
		Private insurance	Killian, 2017
	-	Daily schedules	McAllister et al., 2006
		The physical characteristic of oral medication (Inability to swallow oral medications)	McAllister et al., 2006
		Medicaid insurance	Olivia et al., 2013
		Time on the wait list of between 2 and 3 months	Olivia et al., 2013
	±	None	
	NS	None	
Social opportunity	+	Parental education of a college degree or more	Killian, 2017
		Two parents in the homes, including blended families	Killian, 2017
		Social support (Family, friends, and community support, satisfaction with support)	McAllister et al., 2006; Grady et al., 2019
		Parent-reported attention concerns in the children	Wolfe et al., 2020
		Other psychosocial stressors, parental	Killian, 2017
	-	Families' conflicts before transplantation	Killian, 2017
		Difficulty communicating in the family before transplantation	Killian, 2017
		Race (black race)	Olivia et al., 2013

Oral medication Adherence			
COM-B subcomponents	Relationship	Factors	Sources
	±	Expectations from the others	McAllister et al., 2006
	NS	None	

Table 4, Described factors associated with injection adherence.

*Note: “+”, direct relationship; “-”, inverse relationship; “±”, inconsistent relationship; “NS”, not significant factors

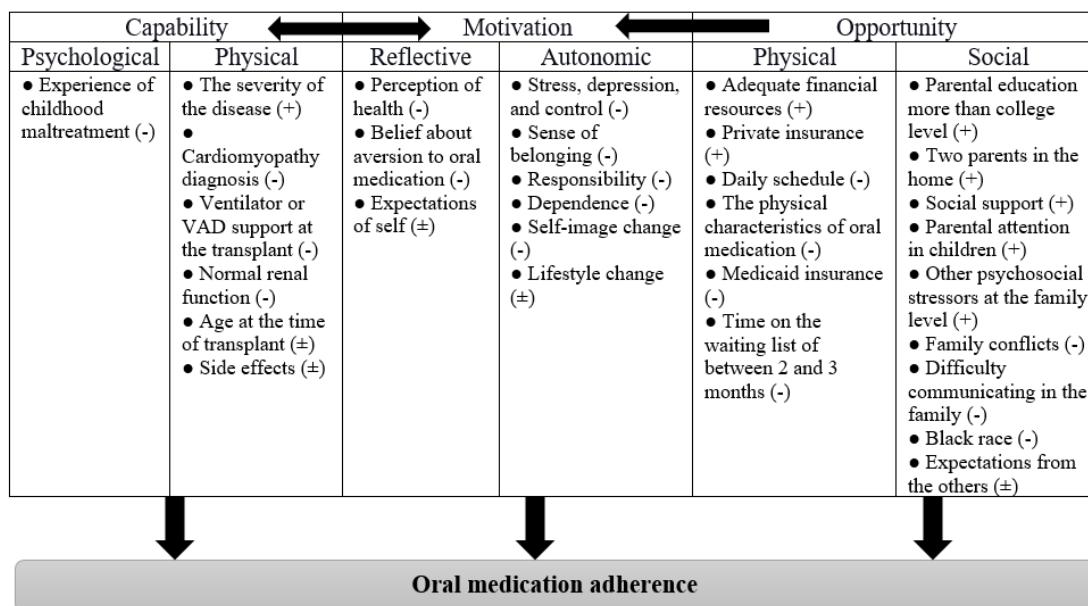


Figure 4, Illustrated a framework of factors associated with oral medication adherence by using the COM-B model of behavior change.

* Note: “+”, direct relationship; “-”, inverse relationship; “±”, inconsistent relationship

The outcome of medication non-adherence

For the outcome of medication non-adherence, there was only one study that reported the outcomes of medication non-adherence in children with heart transplantation. Olivia et al. (2013) found that non-adherence to immunosuppressive medication could influence patients to reject grafts from donors. The risk of graft loss at 1 year and 2 years were 27% and 35%, respectively, after the first report of non-adherence. Moreover, Olivia et al. found that 7 graft loss events among participants had re-transplantation. For mortality, the risk of mortality was increased up to 26% in the non-adherence group after first reported at 1 year. Moreover, it would dramatically raise to 33% in 2 years. In this study, 16 participants passed away which was caused by non-adherence (Olivia et al., 2013).

Chapter V

Discussion

This scoping review has synthesized and summarized the included studies regarding medication adherence in children and young adults with cardiovascular disease. The study finding can help healthcare providers to understand the current situation of medication adherence among children and young adults with cardiovascular disease. Moreover, it can also identify gaps in research and practice among this population.

Injectable medication adherence rate, associated factors, and outcomes

In this scoping review, the overall injectable medication adherence was non-adherence in children and young adults with cardiovascular disease. However, in this study, injectable medication adherence was synthesized from secondary antibiotics prophylaxis studies among rheumatic heart disease. So, further study is required to explore more than injection adherence in secondary antibiotics prophylaxis for rheumatic heart disease. According to the result, there were also various factors influencing injection adherence among children and young adults with cardiovascular disease. The capability of participants was an important factor for injection adherence. Besides age, two consistent factors were a part of psychological capability including forgetting and understanding the disease. Forgetting was a psychological factor related to injection non-adherence. Even though Alkan et al. (2022) reported most of the participants adhered to injection medication, the most of non-adherent group reported they forgot to take the

medication and get the prescription. Similarly, the study was conducted on children who were treated with growth hormone therapy. They found that forgetting to take the medication and refill was associated with injection non-adherence (Mohseni et al., 2018). Consideration regarding the characteristics of the patients, most of them were adolescents. Adolescents have a strict daily schedule to attend to and participate in classroom and school activities. So, it is difficult for adolescents to visit the healthcare setting on the weekday for receiving the injection. Moreover, according to the medication regimen, the patients had to receive an injectable medication once a month. Hence, forgetting to take an injection is not an impossible phenomenon for adolescents. Thus, support systems such as alarm systems, flexible health services, etc. were essential to promote injectable medication adherence, especially for patients who forget to take injection medication.

Understanding the disease was a significant factor related to injection adherence (Balbaa et al., 2015). Moreover, this factor can also illustrate the dynamic of the COM-B model. Understanding the disease could influence the motivation of the patients, especially reflective motivation. In this scoping review, the author found that the belief about the necessity of treatment was an inconsistent factor associated with injection adherence. According to the included studies, Balbaa et al. (2015) found that awareness of the consequences of missing prophylaxis doses was directly associated with medication non-adherence. In contrast, the non-adherence group also reported that they consciously chose to miss an injection appointment. Moreover, most non-adherence participants lacked the understanding that injections were required (Engelman et al., 2017). That reflected the intention and knowledge of the participants. If participants had

sufficient knowledge, they would adhere to injection medication. Because the consequences of non-adherence would impact their life. That means they were aware of and believed in the necessity of injection. As aforementioned, the capability (understanding of the disease) can not only influence the behavior (injection adherence) but also influence motivation (belief about the necessity of treatment).

For physical capability, the author found that age was inconsistently associated with injection adherence. The older age at injection was inversely associated with injection adherence. Because it could increase the risk of delivery of injections overdue of more than 35 days (Kevat et al., 2021). On contrary, Alkan et al (2022) found that age was not significantly associated with injection adherence. Similarly, previous studies found that age was not related to injection adherence in rheumatic heart disease patients (Belay et al., 2022; Adem et al., 2020; Musoke et al., 2013). The differentiation between both outcomes was the interval of injections given. In Kevat et al.'s study, even older age at injection was associated with an increased risk of delivery of injections overdue of more than 35 days, it was not associated with an increased risk of delivery of injections overdue of more than 28 days. Following the Australian guideline for the prevention, diagnosis, and management of acute rheumatic fever and rheumatic heart disease 2020, the interval days of delivery of injection should be 28 days (4 weeks) (Ralph et al., 2021).

Other than belief about the necessity of treatment, the motivation factors included belief about aversion to receiving treatment by injection and feeling well. Both were categorized as reflective motivation. For belief about aversion to receiving treatment, low aversion to treatment could improve injection adherence (Alkan et al., 2022). This idea was supported by a previous study. Aversion to needles was the barrier to

maintaining injectable medication in type 2 diabetes (Spain et al., 2016). So, aversion to treatment was an important factor that healthcare providers should not underestimate it. Regarding feeling well and healthy, it could reflect a perception of the health of participants. If the patients felt healthy, it would decrease their motivation to perform the behavior. In this case, the Fijian children with rheumatic heart disease perceived that they were healthy and felt well. So, they thought it was not necessary and did not want to take injections.

Factors categorized under the opportunity of the COM-B model of behavior change were including an increased year of inclusion, time since diagnosis, transport unavailability, medication unavailability, the physical characteristic of injection medication, area of living, treatment clarification, individual or family unit, and ethnicity. Increased the year of inclusion referred to expand the inclusion criteria of the registration system of ARF/RHD. Referring to the included study, an increased year of inclusion was associated with decreased risk of injection delivery overdue more than 28 days. That means the patients could receive resources, raise awareness, easily follow up, and increase delivery of secondary prophylaxis.

For the time since diagnosis, it was associated with injection non-adherence. That represents the difficulty of chronic illness and care. Even though patients and families were educated regarding the disease, medication, and self-management since diagnosis, treatment adherence would be inadequate because of decreased reinforcement of health promotion, transition period, a distraction from lifestyle or daily schedule, etc (Engelman et al., 2016; Jay et al., 1984). Moreover, in terms of transitioning from children to adolescents, it would increase the risk of non-adherence. Adolescents were a vulnerable

group for non-adherence because of changes in physical, psychological, and social development (Salema et al., 2011; Christie & Viner, 2005; Jay et al., 1984). Hence, health services should be friendly and appropriate for adolescents to advocate and support health-seeking behavior (WHO, 2012). An example of an adolescent-friendly intervention was the mHealth intervention on medication adherence in adolescents with asthma. It was successfully improving medication adherence because it was comprised of weekly monitoring, short-time education, a reminder system, consultation, etc. (Kosse et al., 2019).

Regarding transportation and medication unavailability, it was relevant to accessibility. In Fiji, a lack of transportation was reported in the previous study in Uganda, both of them were low and middle-income countries. It was reported that the unavailability of transport caused injection non-adherence (Huck et al., 2015). Moreover, Fijian had to spend their time and a lot of money to transport from the house to the healthcare setting for follow-up, especially in the rural area (WHO, 2011). Hence, public policy was an important role in improving adherence among this population. Medication supply shortage was reported in Africa, the Asia-Pacific region, and Central and South America in 2011. 35% of healthcare providers reported that Benzathine penicillin G was insufficient to treat all of the patients (Taubert et al., 2013). Hence, improving Benzathine penicillin G access was a strategy for RHD patients and a challenge for policymakers. Moreover, inadequate Benzathine penicillin G supply was a reason for traveling to other clinics (lost follow-up) and non-adherence (Wyber et al., 2013). Thus, Wyber et al. (2013) recommended three domains of intervention, including technical and clinical research interventions, market interventions and research partnerships interventions, and systems,

policy, and applied research interventions to improve medication accessibility.

For the physical characteristics of injectable medication, the patients would be confronted with pain from the administration of medication that could affect the motivation of the patient to receive the injection next time. Moreover, less experience healthcare providers would decrease injection adherence because they could not perform the injection procedure properly and form the trustworthy in patients. So, even though the characteristics of injection medication were unavoidable, the knowledge, and performance of healthcare providers could be improved to increase medication adherence among rheumatic heart disease patients. Furthermore, the clarification of treatment was also necessary. Alkan et al. (2022) found that enough information was not significant in medication adherence. In contrast, Engelman et al. (2017) reported some patients want more explanation regarding when and how to get an injection medication. However, the proportion of patients who complained regarding further explanations was a minority. Because 90% of respondents reported explanations were understandable in the quality assessment of injection health services (Engelman et al., 2017). By the way, even though this problem might not have a big effect on adherence, healthcare providers should consider this issue because it could decrease motivation and behavioral performance in rheumatic heart disease patients.

The area of living was also categorized under the opportunity component and inconsistent factor. The resident who resided in the urban area had adequate adherence in Fiji. On the contrary, others reported this factor was not related to injection adherence. However, one study was conducted in Australia which was a high-income country (Kevat et al., 2021). In Turkey's study, most of the participants reported they did not have a

problem reaching medication and hospitals (Alkan et al., 2022). As above, the Fijians who resided in a rural area had to spend their time and money to access the medication and hospital because of medication unavailability. That is why living in an urban area could improve injection adherence in Fiji. However, Fiji RHD Control and Prevention program was currently promoting several activities to enhance injection adherence, including sufficient medication supply, providing education regarding the disease; medication; self-management, etc. (Engelman et al., 2017).

Regarding ethnicity, this factor was an inconsistent relationship with injection adherence in this scoping review. Even though Australia's study was conducted among the indigenous population (Aboriginal and/or Torres Strait Islander Background), ethnicity was not an associated factor with injection adherence (Kevat et al., 2021). It might be the context of socioeconomic and environmental factors influencing non-adherence rather than ethnicity in this population. In contrast, Fiji's study found that the non-iTaukei ethnicity was associated with good adherence. The reports regarding the difference between iTaukei (Fijians) and non-iTaukei (Fijian Indians) were scarce in terms of adherence research. However, some previous studies found that the differences between both groups were the response to pneumococcal vaccination (Boelsen et al., 2019); the incidence of meningitis (Biaukula et al., 2012), and pneumonia (Magree et al., 2005); etc. That might reflect the complexity of sociocultural and environmental factors (Engelman et al., 2016).

Oral medication adherence rate, associated factors, and outcomes

Overall, oral medication adherence was adequate in children and young adults with cardiovascular disease. However, all of the studies were conducted on heart transplantation patients. So, oral medication adherence might refer to immunosuppressive medication adherence. Referring to synthesized results, one factor was categorized under the psychological capability subcomponent. Six factors were categorized under the physical capability subcomponent, including the severity of the disease, cardiomyopathy diagnosis, ventilator or VAD support at the transplant, normal renal function, age at the time of transplant, and side effects. The experience of childhood maltreatment was associated with medication non-adherence (Killian, 2017). The previous study found that maltreatment in childhood was associated with brain development and mental illness (Teicher et al., 2016). Moreover, a previous systematic review reported that adverse childhood experiences (ACEs) had a relationship with treatment non-adherence in adolescents, particularly histories of maltreatment and neglect (Draxler & Ruppar, 2022). Hence, the experiences of maltreatment in childhood were associated with mental disorders and medication adherence, respectively. Similarly, the component under the COM-B model is that capability (experience of childhood maltreatment) influenced motivation (mental illness) and behavior (medication adherence), sequentially. Therefore, children who experienced childhood maltreatment should be closely monitored and assessed for their neuropsychological status, and medication adherence for early detection and poor consequences reduction.

The degree of severity of the disease during pre-transplantation was associated with oral medication adherence after transplantation. The history of intensive care unit

hospitalization was significantly related to and receiving life support during being listed for a transplant could predict immunosuppressive medication adherence during post-transplantation (Killian, 2017). Previous studies supported this idea, the severity of the disease would come with the complexity of medical regimen and care. That might extrapolate that the patients would be influenced by a serious medical problem (Rianthavorn et al., 2014). It would motivate the patients and parents to be aware of life-threatening diseases, and necessarily of treatment and maintain medication adherence. Moreover, the severity of the disease would improve adherence reaching the maximum rate and then diminishing. However, the reason for the diminishing rate of adherence was unknown but it would be speculated that it was discouragement, exhaustion of parents, etc. (Nevins, 2002). Nevertheless, the severity of the disease conflicts with time on the waiting list of between 2 and 3 months in physical opportunity. Logically, spending prolonged time on the waiting list should motivate the patients and parents to be aware of life-threatening diseases, and necessarily of treatment and maintain adherence to medication similar to the severity of the disease but it was not. The reason for oral medication non-adherence would be the exhaustion and desensitization of the patients and families after waiting for transplantation. Due to less evidence to support this reason for the conflict between two factors, further study is needed to explain the relationship between time on the waiting list and medication adherence, and conflict with the severity of the disease.

For cardiomyopathy diagnosis, even the included study reported that the patients who were diagnosed with cardiomyopathy had poor adherence (Olivia et al., 2013), but most of the participants in the adherent and non-adherent groups were diagnosed with

cardiomyopathy. Thus, the author deemed that it was not a significant factor in oral medication non-adherence. Regarding ventilator or VAD support at the transplant, there was no previous research studying the relationship between invasive hemodynamics support and ventilation and medication adherence. Renal dysfunction was common in heart transplant patients and could occur in 68% of patients before 10 years (McCartney et al., 2017). Besides, a study conducted on patients after heart transplantation found that cyclosporine A was associated with renal dysfunction more than tacrolimus in the first 6 months after the transplant (Helmschrott et al., 2015). Moreover, a Genome-wide association (GWAS) study found that two variants (rs17033285, and rs4917601) in gene LINC01121 and a pseudogene BTBD7P2 were associated with glomerular filtration rate (eGFR) after 1 year of transplantations (Asleh et al., 2018). There were various factors influencing renal function after transplantation. However, there was no evidence of a relationship between medication adherence and renal function. Unfortunately, there was no evidence to support their relationship with medication adherence. Hence, future research is necessary.

Age at the time of transplant was inconsistently associated with oral medication adherence. Killian (2017) found that age at the time of transplant was associated with oral medication adherence in children with heart transplantation. Moreover, it could potentially predict rated as adherent in oral medication after transplantation. In contrast, he also found that increased age at the time of transplant was associated with non-adherence after transplantation. Similarly, Olivia et al. (2013) found that the age of 12 to 17 years at the time of transplant was associated with non-adherence. The adolescent age at the time of transplants was associated with medication non-adherence. The adolescent

age was a transitional period from dependence to independence and they made their decision by themselves (Phillips et al., 2018). During this period, alterations in biological and psychological development influenced medication non-adherence in adolescent patients (Hsu, 2005). The previous qualitative study conducted on adolescent and young adult heart transplant recipients found that the poor adherent group never felt independent and normal. In contrast, the good adherent group felt independent and achieved normality similar to early adulthood (Lawrence et al., 2008). So, it is a challenge for healthcare providers to carefully monitor adherence among adolescent and young adult patients.

The side effect was one of the factors related to medication adherence in children and young adults with heart transplants. McAllister et al. (2006) found that the non-adherent group stated that they were confronted with side effects such as acne, hair growth, and stomach aches. On the contrary, the adherent group had no negative side effects from medication. It could speculate that when the patients faced negative side effects from medication, it would decrease their motivation to adhere to medication like the mechanism in the COM-B model. Thus, healthcare providers should closely monitor and change the medication regimen to treat the patients to decrease the side effects and increase medication adherence.

Regarding motivation, two studies reported ten associated factors with oral medication adherence. Four factors were categorized under reflective motivation such as perception of health, belief about aversion to oral medication, and expectations of self. A study conducted on adolescents with heart transplants reported that non-adherents stated feeling healthy was the reason for missing the medication (McAllister et al., 2006). Feeling healthy could reflect the perception of the patient toward their health. If the

patient perceived that they had good health status, they might choose to miss the medication. According to McAllister et al.'s study, non-adherent faced side effects, aversion to oral medication, low sense of belonging, and disruption of lifestyle from taking medication and heart transplantation. So, if they perceived that they had good health, they might choose to miss the medication for eliminating side effects, avoid the feeling of aversion toward oral medication, increase their sense of belonging, and decrease lifestyle changes. However, this perception could affect their health, especially heart transplant patients. Because if they choose to miss the medication, they might have graft rejection within 1 year after the non-adherence event (Olivia et al., 2013). Thus, healthcare providers should provide information regarding the importance of taking medication following the physician's recommendation even if they have or perceive that they have good health status. Because taking medication is not only to improve their health status but also sustain their health and graft.

Aversion to medication is a common problem in pediatric patients as well as some adult patients (Mennella et al., 2013; Mennella & Beauchamp, 2008). Referring to the included study, McAllister et al. (2006) found that non-adherent patient stated the reason for missing medication was an inability to take oral medication. She stated that she could not take medication at all before transplants and had to take an hour to take medication. That could reflect the belief about aversion to oral medication. Aversion to medication could reflect negative feelings or beliefs toward medication, for instance, children oppose taking oral medication because of its taste. This factor was influenced by the factor under the opportunity component "the physical characteristics of oral medication". According to the COM-B model, the opportunity component could influence behavior and

motivation as well. In this situation, the physical characteristics of oral medication (opportunity) such as taste, shape, route, etc. could increase aversive feelings (motivation) toward oral medication. Hence, healthcare providers should be aware of this situation and provide an appropriate solution for this problem such as changing the form of medication, consulting with parents to find out the solution, etc. Even though this problem could not be avoided in some patients, healthcare providers should provide enough information regarding the necessity of taking medication to patients and families and closely monitor every patient to decrease non-adherence and poor consequences from missing medication.

For the expectation of self, a study conducted on adolescents after heart transplant reported that the non-adherent group had lowered expectations of self in comparison with the adherent group (McAllister et al., 2006). Expectations of self were affected by heart transplants in terms of physical changes influencing their perspective on their function. According to the COM-B model, capability could influence motivation. Lowered expectations of self reflected the evaluation of their function changing from heart transplantation and decreased their motivation to do something. In the included study, the patient decreased their expectations of herself and used it to be the reason for missing medication. This factor could also reflect the perception of health and illness. Because if they perceived that they are so unhealthy or ill that they cannot do anything like before, they would decrease their expectations of themselves. Moreover, accumulated stress from the lowered expectations of self could also affect their mental health. Hence, interventions to improve self-expectation and self-esteem are important in non-adherence patients for self-efficacy, mental health, and adherence improvement.

Regarding automatic motivation, six factors were categorized under this component. Stress, depression, and control were related to medication non-adherence in adolescents after transplantation (McAllister et al., 2006). The previous study found that adherence to immunosuppressive medications was a bidirectional relationship with depression, stress, and anxiety in post-kidney transplantations (Uyar, 2022). Moreover, other studies also found a relationship between oral medication adherence and mental health problems such as coronary heart disease (Fan et al., 2021), hypertension (Kretchy et al., 2021), etc. Hence, healthcare providers should assess the mental status of every patient before starting treatment for promoting adherence, prognosis, and quality of life. In addition, a study conducted on young African American women with hypertension found that depression was associated with the perception of illness as well (Spikes et al., 2020). This study could illustrate the new dynamic within the COM-B model that the motivation not only influences the behavior and capability but also influences each other within the same component. In this case, depression (automatic motivation) influenced the perception of illness (reflective motivation).

A sense of belonging was associated with oral medication non-adherence. According to McAllister et al. (2006), the reason for missed oral medication in adolescents after heart transplantation was a desire to be part of a group and not stand out in school. This study's findings could reflect the sense of belonging in the non-adherent group. Sense of school belonging contains the accepted, respected, included, and engaged feeling in students with others in school (Delker et al., 2020; Anderman & Freeman, 2004). Previous research found that a strong sense of belonging decreased the risk of engaging in risky behavior and increased favorable behavior (Bond et al., 2007;

Schaps & Solomon, 2003). Sense of belonging could influence the performance of behavior in two-way. For instance, referring to McAllister et al.'s study, if the patients felt a low sense of belonging with the others in school, they might not adhere to medication because of an increasing sense of school belonging in terms of not standing out from the others. On the other hand, if the patients sensed that they felt belonged with the others in school even though they were transplants or taking medication in a public space, the adherence behavior would be constructed automatically. Hence, appropriately promoting a sense of school belonging in adolescents could help patients to perform adherence and not do unhealthy behavior.

Responsibility was reported as having an inverse relationship with medication adherence. McAllister et al. (2006) found that adolescents after heart transplantations stated that they had to take complete responsibility for medication. If they forgot to take medication, no one knew it. This factor was relevant to the dependence issue. McAllister et al. (2006) also found that adolescents who were oral medication non-adherence had dependence issues with physicians. Obviously, if the patients had sufficient responsibility and were strong enough to be independent of the other, they would adhere to oral medication and be able to take care of themselves. For self-image change, a study conducted on adolescents after heart transplants found that the non-adherent felt that their image changed from normal people to people with transplants (McAllister et al., 2006). The aspect of the patient on their self-image was an important factor influencing their health. Several previous studies found that self-image, not only body but also perspective, had a relationship with emotional and behavioral problems (Ren et al., 2018; Griffiths et al., 2011). As above, mental health problem was related to medication non-

adherence. So, healthcare providers, and parents should be aware of the self-image of their patients or child and find an appropriate intervention to improve their self-image, self-acceptance, self-esteem, etc. to increase medication adherence, respectively.

Lifestyle change was an inconsistently associated factor with medication adherence depending on the degree of change and affecting the lifestyle in adolescents with heart transplantation (McAllister et al., 2006). Apparently, taking medication following the schedule could interrupt their normal lifestyle and daily schedule, especially adolescents. Adolescents were in a transitional period from dependence to independence (Phillips et al., 2018). Moreover, they have a strict daily schedule to attend and participate in classroom and school activities. So, perception, flexibility, and self-acceptance were important roles in the adaptation of the adolescents who had to take the medication. The patient would accept and adapt their lifestyle if they think that taking medication was important to their health and quality of life. Thus, providing knowledge about the necessity of medication or intervention to promote lifestyle change is important for adolescent patients to enhance oral medication adherence.

For the opportunity component, financial resources were dramatically affecting medication adherence in this scoping review. According to the included studies, adequate financial resources were associated with medication adherence in children and young adults with heart transplantation, especially private insurance (Killian, 2017). In contrast, Medicaid insurance was associated with oral medication non-adherence (Olivia et al., 2013). The difference between the two studies is the type of financial resources. Medicaid insurance was federal and state program for uninsured patients to receive the financial resources for healthcare costs (Lyon et al., 2014). Even though the patient received

healthcare cost support from the government, the transportation cost was also important for medication adherence. Lacking transportation costs would influence medication and treatment adherence, particularly among residents in rural areas. Similarly, the previous study found that poverty and transportation were associated with medication non-adherence (Hensley et al., 2018). Hence, accessibility and distribution of healthcare settings and facilities were necessary for improving medication adherence, especially for poor people or residents in rural areas.

The social opportunity was mainly comprised of parental, family, and other factors. The characteristics of the family were described to be associated with oral medication adherence in adolescents after transplantation. Parental education more than college and two parents in the home were related to oral medication adherence (Killian, 2017). These factors were supported by previous studies that low maternal educational levels less than high school (Wang et al., 2022) and single-parent households (Killian et al., 2018) were associated with oral medication non-adherence in pediatric patients. Moreover, social support from family, friends, and the community was associated with medication adherence in adolescents after heart transplantation (Grady et al., 2019; McAllister et al., 2006). This factor might be supported by the factor within the same subcomponent 'parental attention'. Wolfe et al (2020) found that parental attention in children was associated with oral medication adherence in children after transplants. In contrast, the problematic environment in the family was inversely associated with oral medication adherence. Killian (2017) found that conflicts and problems in communication in families influenced children to be non-adherence to oral medication. It was supported by the studies conducted on children with transplants that family

cohesion and fewer family conflicts were associated with oral medication adherence (Killian et al., 2018). As above, sufficient support from family was an important factor affecting oral medication adherence. Hence, the patients who were suspected of having problematic environments in the family should be carefully assessed, monitored, and prevented from the consequences of that issue to decrease the probability of non-adherence after transplantation. However, Killian (2017) also found that other psychosocial stressors in the family such as impending divorce, problems with housing, death of a family member, etc. was associated with oral medication adherence. It would be assumed that stressors not only decrease motivation but also stimulated the motivation to adhere to oral medication. Hence, healthcare providers should be concerned regarding oral medication adherence among patients with psychological problems in the family whether it was affecting them or not. For race/ethnicity, African American was associated with oral medication non-adherence (Olivia et al., 2013). On the contrary, a systematic review conducted on pediatric organ transplantation found that race/ethnicity was an inconsistently associated factor with oral medication adherence (Killian et al., 2018). Hence, we could not solely use race/ethnicity to identify the adherence status. We should consider other factors such as socioeconomic status, environment, development, etc.

For consequences of medication non-adherence, graft rejection, risk of mortality, and death were reported in the included study. Similarly, the previous study found that adolescent transplant recipients had an incidence of graft rejection than all other groups (Dipchand & Laks, 2020; McDonagh et al., 2009). Hence, medication non-adherence was an important issue for children and young adults. Lacking understanding, underestimating, and unawareness from healthcare providers would affect the quality of

life, and be life-threatening for children and young adult patients who were administered oral medication.

Referring to the previous study regarding applying the COM-B model of behavior to factors associated with adherence (Jackson et al., 2014). Some factors in this scoping review were similarly categorized under the COM-B model with Jackson et al.'s framework such as comprehensive of disease, perception of illness, belief about treatment, accessibility, etc. So, the COM-B model was deemed to be applicable for applying to analyze the factors associated with adherence. However, the author found it difficult to categorize some factors under the COM-B model, for instance, pain from injection might refer to aversion to treatment. However, the author realized that pain from injection was implied to effect by the physical characteristics of medication in terms of route and form. That differed from aversion to treatment. It was a feeling and belief regarding the treatment that influenced the patients to avoid the treatment. Thus, even though the COM-B model was applicable for adherence research and practice, the analysis procedure should be carefully performed when we applied the COM-B model of behavior. The author would exemplify this problem with the previous study. Mersha et al (2020) applied the COM-B model to analyze the factors associated with adherence to nicotine replacement therapy. They categorized social support into social opportunity components. That conflicted with the framework from Jackson et al. (2014). Jackson et al. categorized social support into the physical opportunity components. The difference between the two reports was the definition of each subcomponent. Jackson et al. (2014) defined social opportunity as the cultural milieu that dictates the way people think about things. On the other hand, Mersha et al. (2020) defined social opportunity as the factors

outside the individual that makes the performance of the behavior, and it was not the physical environment. Hence, this scoping review applied the definition from the original developer of the COM-B model of behavior change (West & Michie, 2020).

Strengths and limitations of the study

The current study is the first scoping review containing medication adherence regarding children and young adults with cardiovascular disease and provides the board review regarding this topic including medication adherence rates, factors, and outcomes. This study applied the COM-B model of behavior change to analyze and map the factor in each subcomponent for easy understanding. That could be useful for policymakers, researchers, and healthcare providers to create intervention, research, and public policy which directly benefits children and young adults with cardiovascular disease, and non-adherence patients.

This scoping review used the eligible criteria for screening the included studies with the systemic process. So, most of the included studies were good candidates for the research question. On the other hand, strict criteria and the systemic process could not guarantee that all of the eligible studies were retrieved from the database. This review included only English language study. So, the other language was excluded. That means there were some studies from non-English speaking countries probably excluded from this review. Moreover, this study did not include the gray literature such as conference proceedings, unpublish studies, etc. Hence, this study has publication bias because gray literature was excluded (Paez, 2017).

According to the characteristics of an individual source of evidence, various

studies from various countries were included in this study. However, there were no studies from Europe and South America. For rheumatic heart disease patients, there were no studies in North America, South America, and Europe. So, the study finding would be concerned with implications for rheumatic heart disease patients in any country on that continent. In heart transplantation patients, all studies were only conducted in North America (the United States). Thus, further studies were needed in different contexts and countries. Even though the included studies were comprised of several methods, various patients' characteristics, and study findings, there were some overlapping study findings. Hence, the result of this scoping review was applicable and could be applied to future research, practice, and policy.

For inclusivity, we included all populations who were children and young adults with cardiovascular disease. So, the included studies were conducted among both the majority and indigenous populations. Thus, it would be applicable for healthcare providers, researchers, and policymakers to apply the study result to both groups. However, each indigenous group had their own norm, tradition, and culture. Hence, applying study results to an indigenous population should be carefully applied for research and practice.

Referring to the study findings, some inconsistent factors were reported. Applying inconsistent factors in research and practice should be considered regarding patients' characteristics and contexts. Even though some factors were supported by several pieces of evidence in a similar direction, generalizing factors should carefully apply to future research and practice. Because the majority of patients were only rheumatic heart disease and heart transplantation patients.

The last limitation is categorizing some factors under the COM-B model of behavior change. Throughout the analytic process, I found that some factors were difficult to firmly categorize under a particular subcomponent. For example, non-adherent children with heart transplants stated that a major psychological barrier to taking medication was an inability to swallow oral medication. It can refer to aversive feelings toward oral medication because they spend an hour taking pills. On the other hand, it can refer to the physical characteristics of medication because they mention an inability to swallow the oral medication. In this review, I analyzed and categorized it into two factors, including belief about aversion to oral medication, and the physical characteristics of oral medication. Similarly, a previous study found that it was difficult to make a solid judgment on categorizing the determinants following the COM-B model. They exemplified the case of “self-efficacy”. It could be categorized under psychological capability in terms of “knowledge or psychological skills, strength, etc.” and could also categorize under reflective motivation in terms of “evaluation about oneself” (Whittal et al. 2021). So, categorizing factors under the subcomponents within the COM-B model of behavior change should carefully categorize and always consider the definition of each subcomponent for correction, easily understanding the dynamic between factors, and applicable in practice and research.

Implication for research, practice, and policy

Even though several factors are identified as having significant associations with medication adherence in this scoping review, some of them do not have evidence to support the relationship between that factor and medication adherence. Besides, integrating all of the factors and examination is required because the included studies are having different types of study designs, methodology, analysis, etc. Moreover, the author recommends using the COM-B model of behavior change to be a conceptual framework for easy understanding, and implementation in research, practice, and policy development. Following the COM-B model, there are several factors under the applying the COM-B model of behavior to factors associated with adherence not found in this scoping review (Jackson et al., 2014). Furthermore, the author suggests examining the study findings because some factors lacked information from the patient's view. On the other hand, some factors from qualitative data are needed to examine to find the statistically significant. However, the study finding could guide the healthcare researcher to conduct the research or to be evidence to support their study outcome. For instance, the study findings can be used to be evidence for study in the indigenous population.

The study finding can be used in clinical practice to facilitate the healthcare provider to easily identified the risk factor, early warning, and early prevention and remedy the causation. Because the study findings were reviewed and integrated from several studies from several sources of evidence using the eligibility criteria to screen and include in this study. Moreover, healthcare providers can use associated factors to construct the program or intervention to promote medication adherence in clinical practice. As above, this scoping review identified several factors that were relevant to

public and health policy such as accessibility, financial resources, medication regimen, etc. Hence, applying this study's findings could help policymakers and healthcare professionals to understand the overview situation of medication adherence and generate an appropriate program or policy for children and young adults with cardiovascular disease who were non-adherence.

Chapter VI

Conclusion

Most of the children and young adults with cardiovascular disease in this scoping review were adhering to oral medication but not adhering to injectable medication.

There were 15 factors associated with injection medication adherence such as understanding the disease, perception of health, etc. There was only one factor under physical capability (e.g., age) and no factor under automatic motivation. For factors associated with oral medication adherence, there were 31 factors within this theme such as the experience of childhood maltreatment, the severity of the disease, etc. Most of the factors were mapped and identified following the definition of subcomponents under the COM-B model of behavior change. However, most of them required further research to validate in practice and research.

The study regarding the outcomes of medication adherence was scarce. The strength of this study is the first scoping review about medication adherence in children and young adults with cardiovascular disease, is useful for policymakers, and healthcare professionals to create a strategy and intervention for promoting adherence in this population, and is applicable for applying the study result with the major and indigenous population. The study finding can be used in clinical practice to facilitate the healthcare provider to easily identified the risk factor, early warning, and early prevention and remedy the causation of medication non-adherence. This study recommends using the COM-B model of behavior change for further research, practice, and policy development for easy understanding, and implementation.

References

- Anagnostopoulou, A. (2023). The burden of obesity in children with congenital heart disease. *Global Pediatrics*, 3, 1-8. <https://doi.org/10.1016/j.gped.2023.100037>
- Adem, A., Dukessa Gemechu, T., Jarso, H., & Reta, W. (2020). Rheumatic Heart Disease Patients' Adherence to Secondary Prophylaxis and Associated Factors at Hospitals in Jimma Zone, Southwest Ethiopia: A Multicenter Study. *Patient preference and adherence*, 14, 2399–2406. <https://doi.org/10.2147/PPA.S281413>
- Al-Hassany, L., Kloosterboer, S. M., Dierckx, B., & Koch, B. C. (2019). Assessing methods of measuring medication adherence in chronically ill children-a narrative review. *Patient preference and adherence*, 13, 1175–1189. <https://doi.org/10.2147/PPA.S200058>
- Alkan, F., Yigit, E., Sapmaz, S. Y., & Coskun, S. (2022). Clinical and psychosocial factors affecting treatment adherence in children with rheumatic heart disease. *Cardiology in the young*, 32(10), 1668–1674. <https://doi.org/10.1017/S1047951122002189>
- Amarilyoa, G., Chodickb, G., Zalcmanb, J., Korenb, G., Levinskya, Y., Somekha, I., & Harela, L. (2019). Poor long-term adherence to secondary penicillin prophylaxis in children with. *Seminars in Arthritis and Rheumatism*, 48, 1019-1024. [doi:https://doi.org/10.1016/j.semarthrit.2018.10.015](https://doi.org/10.1016/j.semarthrit.2018.10.015)
- Am Coll Cardiol. 2013 Mar, 61 (10_Supplement) E2004. [https://doi.org/10.1016/S0735-1097\(13\)62004-5](https://doi.org/10.1016/S0735-1097(13)62004-5)
- Anderman, L. H., & Freeman, T. M. (2004). Students' sense of belonging in school. In P. R. Pintrich, & M. L. Maehr (Eds.), *Advances in motivation and achievement: Vol. 13. motivating students, improving schools: The legacy of carol midgley* (pp. 27-63). Greenwich, CT: JAI Press.
- Arvind, B., & Ramakrishnan, S. (2020). Rheumatic Fever and Rheumatic Heart Disease in Children. *Indian journal of pediatrics*, 87(4), 305–311. <https://doi.org/10.1007/s12098-019-03128-7>
- Asleh, R., Snipelisky, D., Hathcock, M., Kremers, W., Liu, D., Batzler, A., Jenkins, G., Kushwaha, S., & Pereira, N. L. (2018). Genomewide association study reveals novel genetic loci associated with change in renal function in heart transplant recipients. *Clinical transplantation*, 32(10), e13395. <https://doi.org/10.1111/ctr.13395>
- Balbaa, A., ElGuindy, A., Pericak, D., Yacoub, M. H., & Schwalm, J. D. (2015). An evaluation of secondary prophylaxis for rheumatic heart disease in rural Egypt. *Global cardiology science & practice*, 2015(3), 40. <https://doi.org/10.5339/gcsp.2015.40>
- Barker, F., Atkins, L., & Lusignan, S. d. (2016). Applying the COM-B behaviour model and behaviour change wheel to develop an intervention to improve hearing-aid

- use in adult auditory rehabilitation. *International Journal of Audiology*, 55, 90-98. doi:<https://doi.org/10.3109/14992027.2015.1120894>
- Beaton, A., Aliku, T., Dewyer, A., Jacobs, M., Jiang, J., Longenecker, C. T., Lubega, S., McCarter, R., Mirabel, M., Mirembe, G., Namuyonga, J., Okello, E., Scheel, A., Tenywa, E., Sable, C., & Lwabi, P. (2017). Latent Rheumatic Heart Disease: Identifying the Children at Highest Risk of Unfavorable Outcome. *Circulation*, 136(23), 2233–2244. <https://doi.org/10.1161/CIRCULATIONAHA.117.029936>
- Belay, W., Dessie, A., Ahmed, H., Gedlu, E., Mariyo, A., Shehibo, A., Tigabu, Z., Aliyu, M. H., & Soslow, J. (2022). Secondary prevention of rheumatic heart disease in Ethiopia: a multicenter study. *BMC cardiovascular disorders*, 22(1), 26. <https://doi.org/10.1186/s12872-022-02473-4>
- Best, K. E., & Rankin, J. (2016). Long-Term Survival of Individuals Born With Congenital Heart Disease: A Systematic Review and Meta-Analysis. *Journal of the American Heart Association*, 5(6), e002846. <https://doi.org/10.1161/JAHA.115.002846>
- Best, K. E., Tennant, P. W. G., & Rankin, J. (2017). Survival, by Birth Weight and Gestational Age, in Individuals With Congenital Heart Disease: A Population-Based Study. *Journal of the American Heart Association*, 6(7), e005213. <https://doi.org/10.1161/JAHA.116.005213>
- Bezold, L. I., & Bricker, J. T. (1994). Acquired heart disease in children. *Current opinion in cardiology*, 9(1), 121–129. <https://doi.org/10.1097/00001573-199401000-00015>
- Bjornard, K., Riehle-Colarusso, T., Gilboa, S. M., & Correa, A. (2013). Patterns in the prevalence of congenital heart defects, metropolitan Atlanta, 1978 to 2005. *Birth Defects Research Part A: Clinical and Molecular Teratology*, 97(2), 87-94. doi:<https://doi.org/10.1002/bdra.23111>
- Boelsen, L. K., Dunne, E. M., Mika, M., Eggers, S., Nguyen, C. D., Ratu, F. T., Russell, F. M., Mulholland, E. K., Hilty, M., & Satzke, C. (2019). The association between pneumococcal vaccination, ethnicity, and the nasopharyngeal microbiota of children in Fiji. *Microbiome*, 7(1), 106. <https://doi.org/10.1186/s40168-019-0716-4>
- Bond, L., Butler, H., Thomas, L., Carlin, J., Glover, S., Bowes, G., & Patton, G. (2007). Social and school connectedness in early secondary school as predictors of late teenage substance use, mental health, and academic outcomes. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine*, 40(4), 357.e9–357.e3.57E18. <https://doi.org/10.1016/j.jadohealth.2006.10.013>
- Britten, N., Stevenson, F., Gafaranga, J., Barry, C., & Bradley, C. (2004). The expression of aversion to medicines in general practice consultations. *Social science & medicine* (1982), 59(7), 1495–1503.

<https://doi.org/10.1016/j.socscimed.2004.01.019>

- Burkhart, P. V., & Sabaté, E. (2003). Adherence to long-term therapies: evidence for action. *Journal of nursing scholarship : an official publication of Sigma Theta Tau International Honor Society of Nursing*, 35(3), 207.
- Chaikitpinyo, A., Panamonta, M., Wongswadiwat, Y., Weraarchakul, W., Panamonta, O., Panthongviriyakul, A., & Thepsuthammarat, K. (2014). Rheumatic and congenital heart diseases among school children of Khon Kaen, Thailand: declining prevalence of rheumatic heart disease. *Asian Biomedicine*, 8(5), 645–650. doi:10.5372/1905-7415.0805.339
- Christie, D., & Viner, R. (2005). Adolescent development. *BMJ (Clinical research ed.)*, 330(7486), 301–304. <https://doi.org/10.1136/bmj.330.7486.301>
- Culliford-Semmens, N., Tilton, E., Webb, R., Lennon, D., Paku, B., Malcolm, J., French, S., Blair, N., & Wilson, N. (2017). Adequate adherence to benzathine penicillin secondary prophylaxis following the diagnosis of rheumatic heart disease by echocardiographic screening. *The New Zealand medical journal*, 130(1457), 50–57.
- Delker, E., East, P., Blanco, E., Wu, V., Encina, P., Lozoff, B., Delva, J., & Gahagan, S. (2020). Associations Among Household Chaos, School Belonging and Risk Behaviors in Adolescents. *The journal of primary prevention*, 41(4), 383–396. <https://doi.org/10.1007/s10935-020-00592-2>
- Dipchand AI, Laks JA. Pediatric heart transplantation: long-term outcomes. *Indian J Thorac Cardiovasc Surg*. 2020 Aug;36(Suppl 2):175-189. doi: 10.1007/s12055-019-00820-3. Epub 2019 May 29. PMID: 33061202; PMCID: PMC7538525.
- Draxler, J. M., & Ruppar, T. M. (2022). Treatment Adherence in Adolescents With Histories of Adverse Childhood Experiences: A Systematic Review. *Journal of psychosocial nursing and mental health services*, 60(6), 11–18. <https://doi.org/10.3928/02793695-20211118-04>
- Edgcomb, J. B., & Zima, B. (2018). Medication Adherence Among Children and Adolescents with Severe Mental Illness: A Systematic Review and Meta-Analysis. *Journal of child and adolescent psychopharmacology*, 28(8), 508–520. <https://doi.org/10.1089/cap.2018.0040>
- Engelman, D., Ah Kee, M., Mataika, R. L., Kado, J. H., Colquhoun, S. M., Tulloch, J., & Steer, A. C. (2017). Secondary prevention for screening detected rheumatic heart disease: opportunities to improve adherence. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 111(4), 154–162.

<https://doi.org/10.1093/trstmh/trx035>

- Engelman, D., Mataika, R. L., Kado, J. H., Ah Kee, M., Donath, S., Parks, T., & Steer, A. C. (2016). Adherence to secondary antibiotic prophylaxis for patients with rheumatic heart disease diagnosed through screening in Fiji. *Tropical medicine & international health : TM & IH*, 21(12), 1583–1591. <https://doi.org/10.1111/tmi.12796>
- Fan, Y., Shen, B. J., & Tay, H. Y. (2021). Depression, anxiety, perceived stress, and their changes predicted medical adherence over 9 months among patients with coronary heart disease. *British journal of health psychology*, 26(3), 748–766. <https://doi.org/10.1111/bjhp.12496>
- Fang, J., Wang, J. W., Li, J., Li, H., & Shao, C. (2017). The correlates of social capital and adherence to healthy lifestyle in patients with coronary heart disease. *Patient preference and adherence*, 11, 1701–1707. <https://doi.org/10.2147/PPA.S140787>
- Gotschall T. (2021). EndNote 20 desktop version. *Journal of the Medical Library Association : JMLA*, 109(3), 520–522. <https://doi.org/10.5195/jmla.2021.1260>
- Grady, K. L., Andrei, A. C., Shankel, T., Chinnock, R., Miyamoto, S. D., Ambardekar, A. V., Anderson, A., Addonizio, L., Latif, F., Lefkowitz, D., Goldberg, L. R., Hollander, S. A., Pham, M., Van't Hof, K., Weissberg-Benchell, J., Yancy, C., Liu, M., Melody, N., & Pahl, E. (2019). Pediatric Heart Transplantation: Transitioning to Adult Care (TRANSIT): Feasibility of a Pilot Randomized Controlled Trial. *Journal of cardiac failure*, 25(12), 948–958. <https://doi.org/10.1016/j.cardfail.2019.06.011>
- Griffiths, L. J., Dezateux, C., & Hill, A. (2011). Is obesity associated with emotional and behavioural problems in children? Findings from the Millennium Cohort Study. *International journal of pediatric obesity : IJPO : an official journal of the International Association for the Study of Obesity*, 6(2-2), e423–e432. <https://doi.org/10.3109/17477166.2010.526221>
- Gupta P. (2014). Caring for a teen with congenital heart disease. *Pediatric clinics of North America*, 61(1), 207–228. <https://doi.org/10.1016/j.pcl.2013.09.019>
- Helmschrott, M., Rivinius, R., Ruhparwar, A., Schmack, B., Erbel, C., Gleissner, C. A., Akhavanpoor, M., Frankenstein, L., Ehlermann, P., Bruckner, T., Katus, H. A., & Doesch, A. O. (2015). Advantageous effects of immunosuppression with tacrolimus in comparison with cyclosporine A regarding renal function in patients after heart transplantation. *Drug design, development and therapy*, 9, 1217–1224. <https://doi.org/10.2147/DDDT.S79343>
- Hensley, C., Heaton, P. C., Kahn, R. S., Luder, H. R., Frede, S. M., & Beck, A. F. (2018). Poverty, Transportation Access, and Medication Nonadherence. *Pediatrics*, 141(4), e20173402.

<https://doi.org/10.1542/peds.2017-3402>

- Hoegy, D., Bleyzac, N., Robinson, P., Bertrand, Y., Dussart, C., & Janoly-Dumenil, A. (2019). Medication adherence in pediatric transplantation and assessment methods: a systematic review. *Patient preference and adherence*, 13, 705–719. <https://doi.org/10.2147/PPA.S200209>
- Hsu D. T. (2005). Biological and psychological differences in the child and adolescent transplant recipient. *Pediatric transplantation*, 9(3), 416–421. <https://doi.org/10.1111/j.1399-3046.2005.00352.x>
- Huck, D. M., Nalubwama, H., Longenecker, C. T., Frank, S. H., Okello, E., & Webel, A. R. (2015). A qualitative examination of secondary prophylaxis in rheumatic heart disease: factors influencing adherence to secondary prophylaxis in Uganda. *Global heart*, 10(1), 63–69.e1. <https://doi.org/10.1016/j.gheart.2014.10.001>
- Jay, S., Litt, I. F., & Durant, R. H. (1984). Compliance with therapeutic regimens. *Journal of adolescent health care : official publication of the Society for Adolescent Medicine*, 5(2), 124–136. [https://doi.org/10.1016/s0197-0070\(84\)80012-1](https://doi.org/10.1016/s0197-0070(84)80012-1)
- Kannan B. R. (2020). Clinical Diagnostic Approach to Congenital Acyanotic Congenital Heart Disease in Infants and Children. *Indian journal of pediatrics*, 87(5), 381–384. <https://doi.org/10.1007/s12098-020-03251-w>
- Katchamat, N., Kobayashi, K., Nishigaki, K., Punyoo, J., & Ota, E. (2022). Analysis using the COM-B model of behavior change to medication adherence among pediatrics and young adults with cardiovascular disease: a scoping review protocol. *figshare. Journal contribution*. <https://doi.org/10.6084/m9.figshare.21749255.v1>
- Kevat, P. M., Gunnarsson, R., Reeves, B. M., & Ruben, A. R. (2021). Adherence rates and risk factors for suboptimal adherence to secondary prophylaxis for rheumatic fever. *Journal of paediatrics and child health*, 57(3), 419–424. <https://doi.org/10.1111/jpc.15239>
- Killian M. O. (2017). Psychosocial predictors of medication adherence in pediatric heart and lung organ transplantation. *Pediatric transplantation*, 21(4), 10.1111/petr.12899. <https://doi.org/10.1111/petr.12899>
- Killian, M. O., Schuman, D. L., Mayersohn, G. S., & Triplett, K. N. (2018). Psychosocial predictors of medication non-adherence in pediatric organ transplantation: A systematic review. *Pediatric transplantation*, 22(4), e13188. <https://doi.org/10.1111/petr.13188>
- Kosse, R. C., Bouvy, M. L., de Vries, T. W., & Koster, E. S. (2019). Effect of a mHealth intervention on adherence in adolescents with asthma: A randomized controlled trial. *Respiratory medicine*, 149, 45–51. <https://doi.org/10.1016/j.rmed.2019.02.009>
- Kretchy, I. A., Owusu-Daaku, F. T., & Danquah, S. A. (2014). Mental health in

- hypertension: assessing symptoms of anxiety, depression and stress on anti-hypertensive medication adherence. *International journal of mental health systems*, 8, 25. <https://doi.org/10.1186/1752-4458-8-25>
- Lawrence, K., Stilley, C. S., Olshansky, E., Bender, A., & Webber, S. A. (2008). Further exploration: maturity and adherence in adolescent and young adult heart transplant recipients. *Progress in transplantation (Aliso Viejo, Calif.)*, 18(1), 50–54. <https://doi.org/10.1177/152692480801800110>
- Lyon, S. M., Douglas, I. S., & Cooke, C. R. (2014). Medicaid expansion under the Affordable Care Act. Implications for insurance-related disparities in pulmonary, critical care, and sleep. *Annals of the American Thoracic Society*, 11(4), 661–667. <https://doi.org/10.1513/AnnalsATS.201402-072PS>
- McAllister, S., Buckner, E. B., & White-Williams, C. (2006). Medication adherence after heart transplantation: adolescents and their issues. *Progress in transplantation (Aliso Viejo, Calif.)*, 16(4), 317–323. <https://doi.org/10.1177/152692480601600406>
- McBride, M. G., Burstein, D. S., Edelson, J. B., & Paridon, S. M. (2020). Cardiopulmonary Rehabilitation in Pediatric Patients With Congenital and Acquired Heart Disease. *Journal of cardiopulmonary rehabilitation and prevention*, 40(6), 370–377. <https://doi.org/10.1097/HCR.0000000000000560>
- McCartney, S. L., Patel, C., & Del Rio, J. M. (2017). Long-term outcomes and management of the heart transplant recipient. *Best practice & research. Clinical anaesthesiology*, 31(2), 237–248. <https://doi.org/10.1016/j.bpa.2017.06.003>
- McDonagh, J. E., & Kaufman, M. (2009). Transition from pediatric to adult care after solid organ transplantation. *Current opinion in organ transplantation*, 14(5), 526–532. <https://doi.org/10.1097/MOT.0b013e32832ffb2a>
- McDonagh, L. K., M, S. J., Cassell, J., Curtis, T., Bastaki, H., Hartney, T., & Rait, G. (2018). Application of the COM-B Model to barriers and facilitators to chlamydia testing in general practice for young people and primary care practitioners: a systematic review. *Implementation Science*, 13(130), 1-19. [doi:https://doi.org/10.1186/s13012-018-0821-y](https://doi.org/10.1186/s13012-018-0821-y)
- McLean, W. (2007). Medication adherence initiatives — part I. *Canadian Pharmacists Journal / Revue des Pharmaciens du Canada*, 140(4), 254-261. [doi:https://doi.org/10.3821/1913701X2007140254:MAIP120CO2](https://doi.org/10.3821/1913701X2007140254:MAIP120CO2)
- Mennella, J. A., & Beauchamp, G. K. (2008). Optimizing oral medications for children. *Clinical therapeutics*, 30(11), 2120–2132. <https://doi.org/10.1016/j.clinthera.2008.11.018>
- Mennella, J. A., Spector, A. C., Reed, D. R., & Coldwell, S. E. (2013). The bad taste of medicines: overview of basic research on bitter taste. *Clinical therapeutics*, 35(8), 1225–1246. <https://doi.org/10.1016/j.clinthera.2013.06.007>

- Michie, S., van Stralen, M. M., & West, R. (2011). The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implementation science : IS*, 6, 42. <https://doi.org/10.1186/1748-5908-6-42>
- Mishra, P., Vamadevan, A. S., Roy, A., Bhatia, R., Natic, N., Singh, S., . . . Legido-Quigley, H. (2021). Exploring barriers to medication adherence using COM-B Model of Behavior among patients with cardiovascular diseases in low- and middle-income countries: a qualitative study. *Patient Preference and Adherence*, 15, 1359-1371. doi:<https://doi.org/10.2147/PPA.S285442>
- Mohseni, S., Heydari, Z., Qorbani, M., & Radfar, M. (2018). Adherence to growth hormone therapy in children and its potential barriers. *Journal of pediatric endocrinology & metabolism : JPEM*, 31(1), 13–20. <https://doi.org/10.1515/jpem-2017-0157>
- Müller, S., Kohlmann, T., & Wilke, T. (2015). Validation of the Adherence Barriers Questionnaire – an instrument for identifying potential risk factors associated with medication-related non-adherence. *BMC Health Services Research*, 15(153), 1-12. doi:DOI 10.1186/s12913-015-0809-0
- Musa, N., Hjortdal, V., Zheleva, B., Murni, I., Sano, S., Schwartz, S., & Staveski, S. (2017). The global burden of paediatric heart disease. *Cardiology in the Young*, 27(S6), S3-S8. doi:10.1017/S1047951117002530
- Musoke, C., Mondo, C. K., Okello, E., Zhang, W., Kakande, B., Nyakoojo, W., & Freers, J. (2013). Benzathine penicillin adherence for secondary prophylaxis among patients affected with rheumatic heart disease attending Mulago Hospital. *Cardiovascular journal of Africa*, 24(4), 124–129. <https://doi.org/10.5830/CVJA-2013-022>
- National Center for Health Statistics. (2022). *Underlying Cause of Death 1999-2020*. Retrieved from Centers for Disease Control and Prevention: <https://wonder.cdc.gov/controller/datarequest/D76.jsessionid=74B03822C353C1965ED9A438B621#Query%20Criteria>
- Network, G. B. (2019). *GBD compare data visualization: cause of deaths in 15-49 years from 1990 to 2019*. Retrieved from Institute for Health Metrics and Evaluation: <https://vizhub.healthdata.org/gbd-compare/>
- Nevins T. E. (2002). Non-compliance and its management in teenagers. *Pediatric transplantation*, 6(6), 475–479. <https://doi.org/10.1034/j.1399-3046.149.ptr1s077.1.x>
- Oliva, M., Singh, T. P., Gauvreau, K., Vanderpluym, C. J., Bastardi, H. J., & Almond, C. S. (2013). Impact of medication non-adherence on survival after pediatric heart transplantation in the U.S.A. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation*, 32(9), 881–888. <https://doi.org/10.1016/j.healun.2013.03.008>

- Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Systematic reviews*, 5(1), 210. <https://doi.org/10.1186/s13643-016-0384-4>
- Paez A. (2017). Grey literature: An important resource in systematic reviews. *Journal of evidence-based medicine*, 10.1111/jebm.12265. Advance online publication. <https://doi.org/10.1111/jebm.12265>
- Page, M. J., Moher, D., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., McGuinness, L. A., ... McKenzie, J. E. (2021). PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ (Clinical research ed.)*, 372, n160. <https://doi.org/10.1136/bmj.n160>
- Pearce, C. J., & Fleming, L. (2018). Adherence to medication in children and adolescents with asthma: methods for monitoring and intervention. *Expert review of clinical immunology*, 14(12), 1055–1063. <https://doi.org/10.1080/1744666X.2018.1532290>
- Peters MDJ, Godfrey C, McInerney P, Munn Z, Tricco AC, Khalil, H. Chapter 11: Scoping Reviews (2020 version). In: Aromataris E, Munn Z (Editors). JBI Manual for Evidence Synthesis, JBI, 2020. Available from <https://synthesismanual.jbi.global>. <https://doi.org/10.46658/JBIMES-20-12>
- Puri, K., Allen, H. D., & Qureshi, A. M. (2017). Congenital Heart Disease. *Pediatrics in review*, 38(10), 471–486. <https://doi.org/10.1542/pir.2017-0032>
- Ralph, A. P., Noonan, S., Wade, V., & Currie, B. J. (2021). The 2020 Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease. *The Medical journal of Australia*, 214(5), 220–227. <https://doi.org/10.5694/mja2.50851>
- Rianthavorn, P., Ettenger, R. B., Malekzadeh, M., Marik, J. L., & Struber, M. (2004). Noncompliance with immunosuppressive medications in pediatric and adolescent patients receiving solid-organ transplants. *Transplantation*, 77(5), 778–782. <https://doi.org/10.1097/01.tp.0000110410.11524.7b>
- Ringewald, J. M., Gidding, S. S., Crawford, S. E., Backer, C. L., Mavroudis, C., & Pahl, E. (2001). Nonadherence is associated with late rejection in pediatric heart transplant recipients. *The Journal of Pediatrics*, 139(1), 75–78. [doi:https://doi.org/10.1067/mpd.2001.115067](https://doi.org/10.1067/mpd.2001.115067)
- Ren, L., Xu, Y., Guo, X., Zhang, J., Wang, H., Lou, X., Liang, J., & Tao, F. (2018). Body image as risk factor for emotional and behavioral problems among Chinese

- adolescents. *BMC public health*, 18(1), 1179. <https://doi.org/10.1186/s12889-018-6079-0>
- Rohit, M., & Rajan, P. (2020). Approach to Cyanotic Congenital Heart Disease in Children. *Indian journal of pediatrics*, 87(5), 372–380. <https://doi.org/10.1007/s12098-020-03274-3>
- Rothenbühler, M., O'Sullivan, C. J., Stortecky, S., Stefanini, G. G., Spitzer, E., Estill, J., Shrestha, N. R., Keiser, O., Jüni, P., & Pilgrim, T. (2014). Active surveillance for rheumatic heart disease in endemic regions: a systematic review and meta-analysis of prevalence among children and adolescents. *The Lancet. Global health*, 2(12), e717–e726. [https://doi.org/10.1016/S2214-109X\(14\)70310-9](https://doi.org/10.1016/S2214-109X(14)70310-9)
- Sabaté, E. (2003). *Adherence to long-term therapies: evidence for action*. Retrieved from World Health Organization: <http://apps.who.int/iris/bitstream/handle/10665/42682/9241545992.pdf;jsessionid=9A5DE57817161476483A98B01C9B90EC?sequence=1>
- Salema, N. E., Elliott, R. A., & Glazebrook, C. (2011). A systematic review of adherence-enhancing interventions in adolescents taking long-term medicines. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine*, 49(5), 455–466. <https://doi.org/10.1016/j.jadohealth.2011.02.010>
- Schaps, E., Solomon, D. The Role of the School's Social Environment in Preventing Student Drug Use. *The Journal of Primary Prevention* 23, 299–328 (2003). <https://doi.org/10.1023/A:1021393724832>
- Shamseer, L., Moher, D., Clarke, M., Ghera, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L. A., & PRISMA-P Group (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ (Clinical research ed.)*, 350, g7647. <https://doi.org/10.1136/bmj.g7647>
- Smit-Fun, V. M., & Buhre, W. F. (2019). Heart Failure in Adult Patients with Congenital Heart Disease. *Anesthesiology clinics*, 37(4), 751–768. <https://doi.org/10.1016/j.anclin.2019.08.005>
- Smith P. (2001). Primary care in children with congenital heart disease. *Journal of pediatric nursing*, 16(5), 308–319. <https://doi.org/10.1053/jpdn.2001.26572>
- Spain, C. V., Wright, J. J., Hahn, R. M., Wivel, A., & Martin, A. A. (2016). Self-reported Barriers to Adherence and Persistence to Treatment With Injectable Medications for Type 2 Diabetes. *Clinical therapeutics*, 38(7), 1653–1664.e1. <https://doi.org/10.1016/j.clinthera.2016.05.009>
- Spikes, T., Higgins, M., Lewis, T., & Dunbar, S. (2020). The Effect of Contextualized Racial and Gendered Stressors, Social Support, and Depression on Hypertension Illness Perceptions and Hypertension Medication Adherence in Young African American Women With Hypertension. *The Journal of*

cardiovascular nursing, 35(6), 576–587.
<https://doi.org/10.1097/JCN.0000000000000671>

- Teicher, M. H., Samson, J. A., Anderson, C. M., & Ohashi, K. (2016). The effects of childhood maltreatment on brain structure, function and connectivity. *Nature reviews. Neuroscience*, 17(10), 652–666. <https://doi.org/10.1038/nrn.2016.111>
- Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. (2018). PRISMA Extension for Scoping Reviews (PRISMA ScR): Checklist and Explanation. *Ann Intern Med*.169:467–473. doi: 10.7326/M18-0850.
- Uyar B. (2022). The analysis of immunosuppressant therapy adherence, depression, anxiety, and stress in kidney transplant recipients in the post-transplantation period. *Transplant immunology*, 75, 101686. <https://doi.org/10.1016/j.trim.2022.101686>
- Walsh, K. E., Cutrona, S. L., Kavanagh, P. L., Crosby, L. E., Malone, C., Lobner, K., & Bundy, D. G. (2014). Medication adherence among pediatric patients with sickle cell disease: a systematic review. *Pediatrics*, 134(6), 1175–1183. <https://doi.org/10.1542/peds.2014-0177>
- Wang, C. S., Troost, J. P., Wang, Y., Greenbaum, L. A., Gibson, K., Trachtman, H., Srivastava, T., Reidy, K., Kaskel, F., Sethna, C. B., Meyers, K., Dell, K. M., Tran, C. L., Hingorani, S., Lemley, K. V., Lin, J. J., & Gipson, D. S. (2022). Determinants of medication adherence in childhood nephrotic syndrome and associations of adherence with clinical outcomes. *Pediatric nephrology (Berlin, Germany)*, 37(7), 1585–1595. <https://doi.org/10.1007/s00467-021-05176-8>
- West, R., & Michie, S. (2020). A brief introduction to the COM-B Model of behaviour and the PRIME Theory of motivation. *Qeios*. doi:<https://doi.org/10.32388/WW04E6.2>
- Whittal, A., Atkins, L., & Herber, O. R. (2021). What the guide does not tell you: reflections on and lessons learned from applying the COM-B behavior model for designing real life interventions. *Translational behavioral medicine*, 11(5), 1122–1126. <https://doi.org/10.1093/tbm/ibaa116>
- Wilson, S. E., Chinyere, U. C., & Queenette, D. (2014). Childhood acquired heart disease in Nigeria: an echocardiographic study from three centres. *African health sciences*, 14(3), 609–616. <https://doi.org/10.4314/ahs.v14i3.16>
- Wolfe, K. R., Kelly, S. L., Steinberg, E., Pliego, J., & Everitt, M. D. (2020). Predictors of neuropsychological functioning and medication adherence in pediatric heart transplant recipients referred for neuropsychological evaluation. *Pediatric transplantation*, 24(1), e13615. <https://doi.org/10.1111/petr.13615>

- World Health Organization. Regional Office for the Western Pacific. (2011). The Fiji Islands health system review. WHO Regional Office for the Western Pacific. <https://apps.who.int/iris/handle/10665/207503>
- Wyber R, Taubert K, Marko S, Kaplan EL. Benzathine Penicillin G for the Management of RHD: Concerns About Quality and Access, and Opportunities for Intervention and Improvement. *Global Heart*. 2013;8(3):227–34. DOI: <http://doi.org/10.1016/j.gheart.2013.08.011>
- Wyber, R., Zühlke, L., & Carapetis, J. (2014). The case for global investment in rheumatic heart-disease control. *Bulletin of the World Health Organization*, 92(10), 768–770. <https://doi.org/10.2471/BLT.13.134486>
- Xiang, L., Su, Z., Liu, Y., Huang, Y., Zhang, X., Li, S., & Zhang, H. (2019). Impact of Family Socioeconomic Status on Health-Related Quality of Life in Children With Critical Congenital Heart Disease. *Journal of the American Heart Association*, 8(1), e010616. <https://doi.org/10.1161/JAHA.118.010616>