Health Care Provider-Delivered Adherence Promotion Interventions: A Meta-Analysis

abstract

BACKGROUND AND OBJECTIVE: Improving medical regimen adherence is essential for maximizing the therapeutic potential of treatments for pediatric chronic illness. Health care providers are uniquely positioned to deliver adherence promotion interventions. However, no studies have summarized the effectiveness of health care provider-delivered adherence interventions. The objective of this study was to describe the effectiveness of health care provider-delivered adherence promotion interventions in improving adherence among children who have chronic illness. Data sources include PubMed, PsycINFO, CINAHL, and Scopus. Studies were included if they were randomized-controlled trials of pediatric interventions aiming to increase adherence to the primary regimen for a chronic illness and at least 1 health care provider delivered the intervention.

RESULTS: A total of 35 randomized-controlled studies including 4616 children were included. Greater improvements in adherence were observed immediately after health care provider-delivered interventions ($d = 0.49$; 95% confidence interval, 0.32 to 0.66) than at longer-term follow-up ($d = 0.32$; 95% confidence interval, 0.10 to 0.54). Treatment effect sizes differed across the adherence behaviors measured. There was significant heterogeneity in treatment effects; however, no moderators of treatment effectiveness were identified. This meta-analysis focused on the published literature. In addition, the majority of studies involved children who had asthma and younger children.

CONCLUSIONS: Health care provider-delivered interventions for children who have chronic illness can be effective in improving adherence. Gains in adherence are highest immediately after intervention. Future interventions and studies should include multiple methods of assessing adherence, include active comparators, and address long-term maintenance of adherence gains. *Pediatrics* 2014;133:e1698–e1707

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KEY WORDS

medication adherence, patient compliance, pediatrics, self care, chronic disease, health personnel

ABBREVIATIONS

CI—confidence interval

HbA1c—Hemoglobin A1c

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Although impressive medical advances have led to the development of effective medical treatments for many pediatric chronic illnesses, these treatments are only effective if patients and families adhere to medical recommendations. Unfortunately, rates of medical regimen non-adherence are high, with ~50% of pediatric patients and their families demonstrating non-adherence.¹ Improving medical regimen adherence is of central importance for achieving better medical outcomes for chronically ill children.² Previous meta-analyses and reviews have focused on the effectiveness of behavioral health professionals (eg, psychologists) in implementing pediatric adherence promotion interventions.^{3–5} However, behavioral health services to improve regimen adherence are not always available to, or necessarily wanted by, pediatric patients and families.

Health care providers (eg, physicians, nurses, dietitians) are arguably ideal individuals to implement adherence promotion interventions because of their existing relationships with families, ongoing monitoring of patient's health outcomes, and familiarity with patient's unique treatment needs. Indeed, there have been calls for pediatric health care providers to provide adherence promotion interventions.^{6,7} However, there have been no systematic reviews or meta-analyses of pediatric health care provider-delivered adherence promotion interventions. Such a review could serve as a foundation for development and dissemination of interventions, particularly in the current environment of health care reform. Thus, the primary aim of the current meta-analysis of randomized-controlled trials was to describe the effectiveness of health care provider-delivered interventions in improving pediatric adherence outcomes. The secondary, exploratory aim was to examine moderators of intervention ef-

fectiveness (eg, intervention setting). Based on existing literature,^{3,4} it was hypothesized that health care provider-delivered interventions would demonstrate a medium treatment effect size and that effects would be weaker at follow-up than shortly post-treatment.

METHODS

In July 2012, literature searches covering all years indexed were conducted in PubMed (1996–2012), Cinahl (1937–2012), PsycINFO (1806–2012), ERIC (1966–2012), the Cochrane Library (1991–2012), and Scopus (includes Medline and Embase; 1960–2012) using combinations of relevant terms (Appendix 1). References of review articles and relevant articles were reviewed.

Study abstracts and full-length articles were screened by 2 independent reviewers trained and supervised by the first author. Studies were included if: (1) the study was a randomized-controlled trial, (2) the intervention aimed to increase patient/family adherence to the primary self-managed regimen for a chronic condition, (3) ≥ 1 health care provider (ie, physicians, nurses, dietitians, respiratory therapists, diabetes or asthma educators, nutritionists, occupational therapists, physical therapists, pharmacists) served as an interventionist, (4) $>50\%$ of the intervention content or time involved contact with the health care provider, (5) mean age of participants <18 years, (6) study measured adherence to behaviors targeted by the intervention, (7) study report was written in English, and (8) effect size could be calculated using data in the report or from study authors. Studies were excluded if any of the following criteria were met: (1) goal of the intervention was to change health care provider behavior, (2) intervention was delivered at schools or summer camps, (3) a mental health professional delivered $>50\%$ of the intervention, (4) study measured adherence using a health outcome (eg, hemoglobin A1c) instead of a behavior (eg,

blood glucose monitoring), (5) study report and attempts to contact authors yielded insufficient information to determine whether the study met inclusion/exclusion criteria or to calculate effect sizes, and (6) study report was not in English.

Studies meeting inclusion criteria were coded by the first author for intervention content (eg, educational, behavioral) and format (eg, individual, groups), adherence behavior targeted, adherence measures used, adherence outcome data, and descriptive information about the sample and study design. Information on intervention effectiveness was coded based on study reports or information from the report authors. The second author conducted reliability coding of 20% of the included articles. Following recommendations outlined by the Cochrane Collaboration,⁸ risk for bias was identified across several domains (ie, sequence generation, allocation concealment, incomplete outcome data, selective outcome reporting, other sources of bias). Coding for adequate prevention of knowledge of allocated intervention was excluded because the nature of the interventions allowed participants to be aware of their allocated group (eg, assignment to psychosocial intervention for adherence versus usual medical care).

Analyses

Effect size calculation and other analyses were based on procedures outlined by the Cochrane Collaboration⁸ and Lipsey and Wilson.⁹ All analyses were completed by using Comprehensive Meta-Analysis¹⁰ and SPSS. Cohen's κ ($\kappa = 0.74$) and Pearson's correlation ($r > 0.9$) were used to examine coding reliability. The primary summary effect size measure was Cohen's d . Statistical independence within studies was maintained in the following ways: (1) multiple measures of adherence within studies were averaged so that each

study contributed 1 effect size for the overall analyses, and (2) if a study's results were presented in more than 1 publication, the effect sizes were averaged. Effect sizes for adherence promotion interventions were examined in several ways. First, the overall effectiveness of interventions was examined across studies at post-treatment (ie, mean pre- to post-treatment (mo): 7.3; SD = 6.4, range, 1–24) and follow-up (mean post-treatment to follow-up (mo): 14.1; SD = 20.9, range, 2–72). Follow-up analyses summarized the effectiveness of interventions after excluding those involving a behavioral health provider and interventions reportedly based on theory versus those that were not. Second, intervention effectiveness was examined by types of adherence behavior (eg, completing medication regimen, making environmental modifications) separately at post-treatment and follow-up. The random effects model was used because it was expected that the treatment effects would differ across studies owing to differences in study design, intervention content, and participants. Heterogeneity in the treatment effects was examined by using the Q-statistic. Prespecified subgroup analyses compared treatment effects by intervention type (education only versus other types), number of health care providers delivering the intervention (ie, 1 provider vs >1), setting (clinic versus other settings), format (individual child/family versus group), and adherence outcome measure (self- or parent-report versus other measures). Rosenthal's fail-safe *n* was calculated to address the potential for sampling or publication bias.

RESULTS

Participants and Study Design

In total, 37 reports representing 35 randomized-controlled studies were included (Fig 1). Across all studies, there

were 4616 participants ($M_{\text{sample size}} = 125$; SD = 113). The majority of reports included youth who had asthma ($n = 23$; 62.1%). Others focused on youth who had diabetes ($n = 7$; 18.9%), obesity ($n = 2$; 5.4%), eczema ($n = 2$; 5.4%), or other conditions ($n = 3$; 8.1%; juvenile rheumatoid arthritis, HIV, sickle cell disease). Fifty-six percent of youth participants were male and their average age using reported central tendencies was 7.0 years. In the reports, the primary adherence intervention of interest was compared with treatment as usual ($n = 25$; 67.6%), an alternative active intervention ($n = 11$; 29.7%), or an attention placebo ($n = 1$; 2.7%). Alternative interventions typically included provision of education in a way that placed greater responsibility on patients and their families and involved less interaction with health care providers (eg, education booklet).

Intervention Characteristics

Most adherence promotion interventions were delivered by a single health care provider ($n = 23$, 62%), whereas the remaining were delivered by 2 or more health care providers ($n = 14$; 38%). Most commonly, nurses delivered interventions ($n = 23$; 62%), followed by physicians ($n = 11$; 30%), psychologists ($n = 6$; 16%), health educators ($n = 5$; 14%), dietitians ($n = 3$; 8%), nutritionists ($n = 2$; 5%), social workers ($n = 2$; 5%), case managers/coordinators ($n = 2$; 5%), respiratory therapists ($n = 1$; 3%), and exercise therapists ($n = 1$; 3%). Interventions targeted a variety of adherence-related behaviors: taking medication ($n = 24$; 65%), symptom monitoring ($n = 9$; 24%), dietary changes ($n = 6$; 16%), environmental modifications ($n = 5$; 14%), insulin administration ($n = 4$; 11%), physical activity changes ($n = 2$; 5%), topical treatments ($n = 2$; 5%), and other health behaviors (eg, refilling medication, attending appointments; $n = 3$; 8%).

Intervention content varied across studies. Behavioral interventions (eg, providing families with specific strategies to manage the regimen, such as increasing parental supervision of regimen completion) were most common ($n = 19$; 51%). Educational interventions were next most common ($n = 15$; 40%) and included providing basic information to families about the patient's illness (eg, etiology, course) and the importance of adherence. Approximately one-third ($n = 12$; 32%) of reports tested interventions that aimed to improve patient adherence through health care provider-initiated actions, such as simplifying the treatment regimen or increasing contact with families. Organizational interventions, such as introducing pillboxes or calendars for self-monitoring, were also used ($n = 5$; 14%). Other interventions included facilitating discussion with caregivers about their child's illness and supporting effective caregiver-health care provider interactions ($n = 4$; 11%).

On average, interventions were comprised of 7 sessions or contacts between the health care provider(s) and patients and families (SD = 4 sessions; range, 4–16). Interventions took place in a variety of settings: clinic ($n = 16$; 43%), patient's home ($n = 10$; 27%), phone ($n = 8$; 22%), inpatient ($n = 1$; 3%), emergency department ($n = 2$; 5.4%), and other (eg, postal mail, university research center; $n = 8$; 21.6%). The vast majority of interventions ($n = 28$; 76%) involved both youths and their families. Some interventions targeted only caregivers ($n = 6$; 16%) or only youths ($n = 3$; 8%). Most interventions were delivered to individual patients or families ($n = 25$; 68%), some in a group format ($n = 6$; 16%), and others comprised both formats ($n = 6$; 16%). The majority of interventions were not explicitly grounded in a theoretical framework ($n = 22$; 60%; $n = 4$, unclear whether grounded in theoretical framework). Thirty percent of interventions ($n = 11$)

FIGURE 1
PRISMA flow sheet.

were grounded in a theoretical framework, such as the Health Belief Model,¹¹ social cognitive learning theory,¹² and stages of change model.¹³

Adherence Outcome Measurement

Adherence outcomes were measured by using patient- or parent-report ($n = 30$; 81%), pharmacy records ($n = 6$; 16%), electronic monitoring ($n = 5$; 14%), direct observation ($n = 3$; 8%), physician rating ($n = 3$; 8%), biological assay ($n = 1$; 3%), and other methods (eg, blood glucometer download) ($n = 2$; 5%).

Effect Sizes

Figure 2 contains a forest plot of post-treatment effect sizes. At post-treatment,

there was a medium effect such that participants receiving the health care provider intervention had higher adherence than participants in the control condition ($d = 0.49$; 95% CI, 0.32 to 0.66; $n = 35$). The effect size after excluding studies that included a behavioral health provider was 0.54 (95% CI, 0.33 to 0.75; $n = 28$). The effect size for interventions based on theory was 0.42 (95% CI, 0.31 to 0.53; $n = 11$) whereas those not explicitly based on theory was 0.37 (95% CI, 0.33 to 0.42; $n = 24$). At follow-up, the treatment effect was small ($d = 0.32$; 95% CI, 0.10 to 0.54; $n = 10$). Effect sizes differed across the adherence behaviors measured (Table 1). The largest effect sizes were for medical regimen completion ($d = 0.57$), medication refills ($d = 0.51$), and com-

posite adherence measures ($d = 0.61$). In contrast, other adherence behaviors, including appointment-making ($d = 0.24$), dietary changes ($d = 0.19$), and symptom monitoring ($d = 0.17$) were smaller in size.

Moderator Analyses

To explore the heterogeneity in treatment effects at post-treatment ($Q[34] = 446.1$; $P < .001$) and follow-up ($Q[9] = 57.8$; $P < .001$), analyses were conducted to examine a priori, potential moderators of treatment effects. Intervention type, number of health care providers delivering the intervention, intervention setting, intervention format (individual child or family versus group), and adherence outcome measure did not

FIGURE 2
Forest plot.

significantly account for heterogeneity in treatment effects (all P values $< .02$ for Q -within moderator groups).

Risk for Bias

Potential risk for bias in the studies included in the meta-analysis was

identified by using Cochrane Collaboration's recommendations⁸ (Table 2): adequate allocation generation (89.2%; $n = 33$), adequate allocation concealment (27.0%; $n = 10$), adequate explanation of incomplete outcome data (70.3%; $n = 26$), study reports free of

suggestion of selective outcome reporting (59.5%; $n = 22$), and study free of other problems that could put it at high risk for bias (67.6%; $n = 25$).

Publication Bias

Based on Rosenthal's fail-safe n , 2643 unpublished studies reporting null results would be needed to reduce the overall effect size across studies (ie, $d = 0.49$) to 0.

DISCUSSION

The current meta-analysis indicates that health care provider-delivered interventions for children who have chronic illness can be effective in improving adherence when compared with treatment as usual or alternative interventions. Treatment effects are strongest immediately after intervention and adherence improvements dissipate over time. Intervention effectiveness also differed depending on the adherence behavior measured. Intervention effects were larger when medical regimen completion (eg, ingesting medications) was assessed compared with when dietary change was the outcome. These findings suggest that health care provider-delivered interventions may be more effective for certain adherence behaviors. Other adherence behaviors, such as making dietary and physical activity changes, may require more intensive interventions or

TABLE 1 Effect Sizes

	Post-Treatment			Follow-Up		
	Number of Effect Sizes	Mean Effect Size	95% CI	Number of Effect Sizes	Mean Effect Size	95% CI
Adherence methodology	5	0.34	−0.07 to 0.75	—	—	—
Appointment-making	1	0.24	−0.31 to 0.78	—	—	—
Adherence composite	4	0.61	0.34 to 0.88	—	—	—
Dietary change	9	0.19	0.02 to 0.36	4	0.32	0.17 to 0.48
Environmental change	9	0.35	−0.03 to 0.73	3	−0.03	−0.30 to 0.24
Medical regimen completion	36	0.57	0.30 to 0.84	10	0.32	−0.06 to 0.69
Physical activity	2	0.11	−0.11 to 0.32	—	—	—
Refill	8	0.51	0.24 to 0.78	3	0.11	−0.07 to 0.29
Sedentary behavior	3	0.24	−0.05 to 0.53	1	0.00	−0.31 to 0.31
Symptom monitoring	10	0.17	−0.14 to 0.49	2	0.18	−0.35 to 0.72

—, No follow-up data available.

TABLE 2 Risk for Bias for Included Studies

	Adequate Sequence Generation	Allocation Concealment	Incomplete Outcome Data Addressed	Free of Selective Reporting	Free of Other Bias
Anderson (1989) ³¹	?	?	+	?	?
Berkovitch (1998) ³²	?	?	+	?	?
Berrien (2004) ³³	+	+	+	+	+
Bloomfield (1990) ³⁴	?	?	?	?	?
Bonner (2002) ³⁶	+	?	+	?	+
Brown (2002) ³⁵	+	+	+	+	+
Butz (2005) ⁴⁰	+	?	—	?	?
Butz (2010) ³⁹	+	?	—	?	?
Burkhart (2002) ³⁷	+	?	?	+	+
Burkhart (2007) ³⁸	+	?	+	+	+
Chan (2003) ⁴¹	+	?	?	?	?
DeBar (2012) ⁴²	+	?	+	+	+
Deforche (2005) ⁴³	—	?	+	?	+
Ducharme (2011) ⁴⁴	+	+	+	+	+
Elamin (1993) ⁴⁵	+	?	?	+	+
Farber (2004) ⁴⁶	+	+	+	+	+
Gorelick (2006) ⁴⁷	+	+	+	+	+
Gray (1998) ⁴⁸	+	?	?	+	+
Hederos (2005) ²⁷	+	?	+	?	+
Hederos (2009) ⁶³	+	?	+	?	+
Howe (2005) ⁴⁹	+	?	—	?	?
Hughes (1991) ⁵⁰	+	?	+	?	?
La Roche (2006) ²⁸	+	?	+	?	+
Lawson (2005) ⁵¹	+	+	+	+	+
LeBaron (1985) ⁵²	+	?	?	+	+
McNabb (1994) ⁵³	+	?	+	?	—
Mitchell (1986) ⁵⁴	+	?	+	+	?
Moore (2009) ⁵⁵	+	+	+	+	+
Otsuki (2009) ⁵⁶	+	+	+	+	+
Rapoff (2002) ⁵⁷	+	?	+	+	+
Smith (1986) ⁵⁸	+	?	+	+	+
Staab (2002) ⁵⁹	+	?	+	+	+
Teach (2006) ⁶⁰	+	+	+	+	+
Wilson (1996) ³⁰	+	?	+	?	+
Van Es (2001) ⁶¹	+	+	?	+	?
Watson (2009) ⁶²	+	?	—	+	+

+, Low risk for bias; —, high risk for bias; ?, unclear risk for bias.

interventions delivered by multidisciplinary providers (eg, nutritionists, psychologists specializing in adherence behavior change).

Health care provider-delivered adherence promotion interventions hold great promise and have a number of characteristics that support sustainability and feasibility. First, the overall results (ie, medium-sized treatment effects) are on par with those described in previous meta-analyses of pediatric adherence promotion interventions, the majority of which were delivered by mental health professionals.^{3,4} The use of behavioral interventions may be driving this treatment effect given that

interventions incorporating behavioral strategies are typically most effective at improving adherence^{3,4} and comprised the majority of studies included in the current meta-analysis. Second, interventions focused on changing both child and family member's behavior, which is consistent with the family-centered approach in pediatrics.¹⁴ Third, health care providers have established relationships with patients and families, which could improve families' willingness to engage in adherence promotion interventions. Interventions that improve communication between providers and families will be critical.^{6,7} Fourth, health care providers often al-

ready monitor patient's medical information related to adherence and health outcomes (eg, for patients who have type 1 diabetes, HbA1c), and thus can provide patients with real-time feedback on the consequences of their adherence. Consensus statements for the management of certain pediatric illnesses (eg, asthma), in fact, encourage health care providers to provide adherence or self-management support.¹⁵ Fifth, interventions in the current meta-analysis were delivered in settings that maximized feasibility for patients and families or that capitalized on existing medical system structures. Continued efforts should be made to develop, test, and disseminate health care provider-delivered adherence promotion interventions. If families do not receive adherence promotion interventions from health care providers, a primary alternative would be a referral to mental health professionals (eg, psychologist, social worker). Although these referrals can be useful and can lead to improved medical regimen adherence for some families,^{16,17} many families do not pursue such referrals because of perceived stigma of meeting with a mental health professional, insurance coverage,^{18,19} and, based on our clinical experience, the hassles of attending "extra" appointments.

Given the studies included in this meta-analysis, there are several limitations with implications for future health care provider-delivered adherence promotion interventions. Most studies focused on children who have asthma and younger children. Increased focus on testing interventions for other chronic illnesses associated with high health care costs, low health-related quality of life, and high rates of morbidity, such as type 1 diabetes, is needed.^{20–22} In addition, it will be important to address the unique adherence issues of older youth, including adolescents and young

adults. Because of the common developmental transitions during adolescence and young adulthood (eg, increased independence, living apart from their families of origin), adolescents and young adults require tailored interventions that address these ongoing transitions. Related to intervention and study design, most interventions were not grounded in a broader theoretical approach, which may have limited their comprehensiveness and examination of mechanisms of change underlying adherence improvements. Fewer than half of the interventions were delivered by >1 multidisciplinary provider. However, given ongoing health care reform and broader movements toward providing multidisciplinary care in pediatrics, it will be important to test multidisciplinary interventions in the future. Most studies compared interventions with treatment as usual, which typically does not control for adherence gains owing to the more frequent or lengthy interactions with providers that patients experience in the active intervention group. Adherence outcomes were also often assessed by using patient- and parent-report, which is typically an overestimate.¹ Future studies should consider including an attention control or active comparison intervention and adherence assessments other than self-report.²³

The current results should be interpreted with several limitations in mind. This meta-analysis focused on the published literature across several specialties, including medicine, nursing, and nutrition. Future studies could seek to replicate the current results using unpublished work. There was wide variability in illness populations targeted and treatment effectiveness across adherence behaviors. Although this reflects the current state of the broader literature on medical regimen adherence, future reviews focused on

particular illness populations and adherence behaviors will be essential for advancing the field. For example, adherence may differ across chronic conditions owing to factors such as the symptoms associated with the illness, perceived illness severity, and regimen complexity, and thus each illness may necessitate unique interventions. Because of the number of studies identified for this meta-analysis, a limited number of moderator analyses could be conducted and those that were conducted used aggregated categories. As the literature in this area grows, future reviews will be able to conduct more moderator analyses comparing interventions and interventions delivered by particular provider types or multidisciplinary teams. Also, the length of time between pre- and post-treatment varied between studies, which may have added variability to the treatment effects. Although approximately one-third of the studies assessed adherence at a follow-up period, the lengths of these follow-up periods ranged widely. The long-term effectiveness of health care provider-delivered adherence promotion interventions may differ when a greater number of studies with follow-up are included.

The current findings hold several implications for next steps in developing health care provider-delivered interventions for adherence. Regarding the content and delivery of interventions, it will be important to design programs that are grounded in a theoretical model. In addition, to facilitate the dissemination of adherence interventions into clinical practice, it will be helpful for future interventions to include clear criteria and algorithms for incorporating adherence assessment and intervention into clinical decision-making. Future adherence interventions should also address maintenance of adherence gains beyond the intervention period (eg, addition of

booster sessions for families who need them).

Next steps could then include optimizing adherence and health outcomes by tailoring the intervention content or delivery based on cost and patient need. For example, families could benefit from interventions that address comorbid mental health conditions that inhibit effective self-management.²⁴ Given the trend toward multidisciplinary care for chronic diseases, it will be important for future intervention studies to quantify the degree of contact and collaboration between providers. Once effective interventions are further developed within illness conditions, a modular approach could be used whereby patients who have different illnesses or specific barriers to adherence receive only the specific “modules” they need.^{25,26} When implementing this research, studies should include active comparators (eg, attention control group, alternative intervention), assess adherence using multiple methods beyond self-report alone,²³ and examine other potential moderators of treatment effectiveness (eg, family-provider communication, patient/family characteristics impacting adherence such as psychological functioning and problem-solving abilities). In addition, studies could examine other important outcomes, including the clinical impact adherence improvements have on health and the cost-effectiveness of implementing adherence promotion interventions.^{27–30}

CONCLUSIONS

Health care provider-delivered interventions for children who have chronic illness and their families appear to be effective at improving adherence to prescribed regimens. The findings suggest that clinicians who want to integrate adherence promotion into their practice could consider a number

of intervention formats (eg, in-person and/or phone interventions delivered by multidisciplinary teams) and content (eg, combination of educational and behavioral strategies), which could help to structure provider's interactions with families and add flexibility to care delivery. Adherence interventions that target medication-taking

and refills are more likely to be effective, and ongoing monitoring and booster sessions will be needed to sustain improved adherence. Continuing to develop and deliver health care provider-led adherence promotion interventions could lead to increased patient and family access to needed adherence interventions, better pedi-

atric health outcomes, and health care cost savings.

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APPENDIX 1 Exemplar Literature Search Strategy

Search	Search Term
1	Adherence OR compliance
2	Intervention OR treatment
3	Physician OR nurse OR dietitian OR respiratory therapist OR nutritionist OR school nurse OR occupational therapist OR physical therapist OR pharmacist
4	Chronic illness OR asthma OR diabetes OR cystic fibrosis OR cancer OR hematology OR oncology OR sickle cell disease OR obesity OR epilepsy OR overweight OR transplant OR gastrointestinal disorder OR inflammatory bowel disease OR colitis OR irritable bowel OR pain disorder OR juvenile rheumatoid arthritis OR infectious diseases OR tuberculosis OR HIV OR cardiovascular disease OR abdominal pain OR burn
5	Pediatric OR child OR adolescent
6	1 AND 2 AND 3 AND 4 AND 5