



SYSTEMATIC REVIEW

Synthesizing Core Outcome Sets for outcomes research in cohort studies: a systematic review

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BACKGROUND: Life course studies are designed to “collect once, use multiple times” for observational and, increasingly, interventional research. Core Outcome Sets (COS) are minimum sets developed for clinical trials by multi-stakeholder consensus methodologies. We aimed to synthesize published COS that might guide outcomes selection for early life cohorts with an interventional focus.

METHODS: We searched PubMed, Medline, COMET, and CROWN for COS published before January 2021 relevant to four life stages (pregnancy, newborns, children <8 years, and parents (adults aged 18–50 years)). We synthesized core outcomes into overarching constructs.

RESULTS: From 46 COS we synthesized 414 core outcomes into 118 constructs. “Quality of life”, “adverse events”, “medication use”, “hospitalization”, and “mortality” were consistent across all stages. For pregnancy, common constructs included “preterm birth”, “delivery mode”, “pre-eclampsia”, “gestational weight gain”, “gestational diabetes”, and “hemorrhage”; for newborns, “birthweight”, “small for gestational age”, “neurological damage”, and “morbidity” and “infection/sepsis”; for pediatrics, “pain”, “gastrointestinal morbidity”, “growth/weight”, “breastfeeding”, “feeding problems”, “hearing”, “neurodevelopmental morbidity”, and “social development”; and for adults, “disease burden”, “mental health”, “neurological function/stroke”, and “cardiovascular health/morbidity”.

CONCLUSION: This COS synthesis generated outcome constructs that are of high value to stakeholders (participants, health providers, services), relevant to life course research, and could position cohorts for trial capabilities.

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IMPACT:

- We synthesized existing Core Outcome Sets as a transparent methodology that could prioritize outcomes for lifecourse cohorts with an interventional focus.
- “Quality of life”, “adverse events”, “medication use”, “hospitalization”, and “mortality” are important outcomes across pregnancy, newborns, childhood, and early-to-mid-adulthood (the age range relevant to parents). Other common outcomes (such as “birthweight”, “cognitive function/ability”, “psychological health”) are also highly relevant to lifecourse research.
- This synthesis could assist new early life cohorts to pre-select outcomes that are of high value to stakeholders (participants, health providers, services), are relevant to lifecourse research, and could position them for future trials and interventional capability.

INTRODUCTION

Life course studies are longitudinal population cohort studies that take an interdisciplinary and holistic view of overall health and social wellbeing, and aim to capture antecedents, characteristics, and events on the path to key health outcomes.¹ Designed to “collect once, use multiple times”, they are increasingly intended to support interventional as well as observational research and to increase the return on investment in research.² A strength is their ability to address multiple hypotheses as they arise—meaning that outcomes must effectively be specified “sight unseen”.

Therefore, if life course studies are to support the most impactful research across multiple fields, they need to capture the highest-utility outcomes with the greatest translational potential. However, no systematic methodology exists to prioritize outcomes selection for life course studies. This may be particularly important for new cohorts designing for an interventional capability because trials require clear-cut primary and secondary outcomes that often encompass life course constructs such as quality of life.

This problem has been addressed for clinical trials with the advent of Core Outcome Sets (COS). COS are agreed-upon,

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standardized minimum sets of outcomes that should be reported in all trials in a particular field.³ COS aim to: (1) increase the relevance and consistency of reported outcomes; (2) facilitate efficient research synthesis and reduce research waste; and (3) reduce selection bias in reported outcomes.³ COS are developed using transparent and rigorous consensus methods typically involving multiple stakeholder groups, usually drawn from multiple countries for maximal international applicability.⁴ Stakeholders include patients, parents, family members, clinicians, and allied healthcare professionals as well as researchers to ensure that outcomes are meaningful to the end-users of the research.³ While designed to improve the reporting of clinical trial outcomes and enable evidence synthesis, COS are increasingly being used in other types of research including observational studies.^{5,6} COS could also provide a rigorous and transparent approach to prioritizing and selecting outcomes for life course cohorts planning to embed capabilities for trials.

This review explored the potential of systematically reviewing and synthesizing COS as a means to prioritize and select outcomes for new interventional cohorts in planning. Internationally important cohorts commencing in the last 5 years, notably Born in Bradford Better Start⁷ and ORIGINS,⁸ have already demonstrated the appetite for and feasibility of embedding trials in life course cohorts. This review was conducted ahead of Generation Victoria (GenV), a whole-of-state cross-generational cohort in advanced planning in Victoria (population 6.5 million in 2019⁹), Australia. GenV intends to target all 150,000 Victorian newborns and their parents over two full years, from late 2021, with the primary purpose of creating large, parallel whole-of-state birth and parent cohorts for discovery and interventional research (see refs. ^{10,11} for purpose, design, and procedures). The process of prioritizing and selecting measures¹² for GenV begins with identifying important domains and constructs that align with GenV's life course frameworks,¹ are not present in administrative and clinical datasets,¹³ and could support interventional as well as observational research.

Lacking a clear methodology to achieve this, we designed and undertook the novel conceptualization and systematic review presented in this paper. We reasoned firstly that drawing on COS as one tool for outcomes selection could strengthen causal inference from cohort studies. This could occur not only via embedded trials and other intervention evaluation methodologies but also by enhancing the value of epidemiological techniques such as causal modeling, strengthening the ability of life course cohorts to further knowledge of causation, and solutions.¹⁴ Secondly, we reasoned that, although the driver for any given COS is a specific condition, the outcomes that families and services value most would largely *not* be condition-specific and indeed would show both commonality across COS and relevance to life course research. Thirdly, we believed that this work could be of value to others planning major new birth cohorts internationally, particularly where an international focus is envisaged.

This paper seeks to systematically review COS relevant to life course cohorts, with an initial focus on pregnancy, newborns, early childhood, and adults 18–50 years (the usual age range for parents of young children). It aims to synthesize the core outcomes from existing COS within and across these four life stages, and to identify common, important, and recurring outcomes to be considered for selection in life course studies.

METHODS

Where they were applicable to the literature and data, we conducted the review in accordance with the 2020 PRISMA guidelines¹⁵ (see Supplementary Material 1 for PRISMA checklist).

Eligibility criteria

Papers eligible for inclusion in this review were completed COS for conditions relevant to four life stages: pregnancy, newborns,

children <8 years of age (pediatric), and adults aged 18–50 (the MESH age range relevant to parents of young children, who are often independent participants whose own health and circumstances are tracked in birth cohorts).

Studies were excluded during the title and abstract screening stage if they were preliminary COS research articles or commentary papers, were not in English, or if a full text article could not be sourced. During full text review, we excluded COS that lacked patient/participant involvement, as this is a key component of robust COS development as per the Core Outcome Set-STAnDards for Development (COS-STAD) guidelines.⁴ We also excluded studies that did not use the Delphi consensus method, a standardized consensus method commonly utilized in COS development. The Delphi method ensures anonymity of stakeholders' preferences, avoiding stifling of opinion by loud or expert voices, and provides an iterative decision-making process to generate by consensus a final set of priorities that truly represents the priorities of the group.^{16,17} Lastly, we excluded COS for conditions with an incidence or prevalence of <0.1%, as they would likely affect a very small number of participants in life course studies, which generally aim to create a representative sample of the whole population.

Information sources and search strategy

A search for relevant papers listed in Medline, PubMed, Core Outcome Measures in Effectiveness Trials (COMET),¹⁸ and Core Outcomes in Women's and Newborn Health (CROWN)¹⁹ databases was conducted on January 14, 2021. Full search strategies for Medline and PubMed are available in Supplementary Material 2. The 45 COS listed on the CROWN website were manually screened for eligibility. In the COMET database we used the search function to identify published COS applicable to ages 0–50 to capture all relevant life stages.

Selection process

All articles retrieved from the searches were imported into EndNote and duplicates were removed. One author (E.M. or K.M.) independently screened the remaining papers by title and abstract for inclusion, and then conducted a full text review for methodological reasons for exclusion, as per the eligibility criteria. Studies excluded at full text review are provided, with justifications, in Supplementary Material 3.

Data collection

For each COS, a single reviewer (E.M. or K.M.) extracted the specific condition, its prevalence or incidence, the consensus method used, stakeholders involved, countries involved, the number of core outcomes, and core domains (if applicable). These data are displayed in Table 1.

Synthesis methods

To our knowledge, no systematic review of COS has previously been undertaken, and thus we endeavored to create a process that enabled synthesis across multiple COS. Firstly, we identified an existing taxonomic framework for outcomes by Dodd et al.²⁰ to guide our synthesis process. This framework was chosen as it was designed to be comprehensive, bridge gaps in existing classification systems, and to cover "all potential outcomes from clinical trials".²⁰ We found no other pre-existing framework to compete with this. Moreover, the authors tested this taxonomy by applying it to COS from the COMET database, and thus it was directly applicable to our intended COS synthesis. This taxonomy outlines five key domains for outcomes: (1) Death, (2) Physiological and Clinical, (3) Life Impact, (4) Adverse Events, and (5) Resource Use.

The synthesis process (undertaken by E.M. and K.M.) began by mapping all core outcomes against all the COS in which they appear. Where we deemed necessary, we collapsed terms referring to the same construct into a single category. For

Table 1. Summary of included Core Outcome Sets (COS).

Condition	Incidence (I) or prevalence (P)	Number of stakeholders ^x	Number of countries	Number of core outcomes	Limitations
Pregnancy & Obstetric COS; n = 12					
Epilepsy ²⁹	P = 0.16–0.70% ³⁰	99	1 (UK)	31	a, b, d
Induction of labor ³¹	I = 20% of pregnancies ³¹	86	6	28	b, d
Pre-eclampsia ²⁴	I = 4.2% of pregnancies ³⁰	432	56	22	a
Gestational diabetes (prevention & treatment) ³²	I (Aus) = 16.1% pregnant women have gestational diabetes ³³	173	27	14	a, c
Pre-pregnancy care for pre-gestational diabetes ³⁴	I (Aus) = 16.1% pregnant women have gestational diabetes ³³	151	24	17	a
Fetal growth restriction ³⁵	I = 3–9% pregnancies ³⁶	238	36	22	b
Hyperemesis gravidarum ³⁷	I ≤ 3.6% pregnancies ³⁷	178	22	24	a, b, d
Postpartum hemorrhage (PPH) ³⁸	I = 24.3% of pregnancies; 2% severe PPH ³⁰	205	36	12	a
Infertility ³⁹	I ≈ 11% couples in Australia ⁴⁰	372	41	7	a
Diabetes after pregnancy ⁴¹	I (Aus) = 16.1% pregnant women have gestational diabetes ³³	115	23	50	d
Selective fetal growth restriction in twins ⁴²	I (monozygotic twins) = 0.3% of all pregnancies ⁴³	103	23	11	a, b
Preterm birth ⁴⁴	I = 8.3% ³⁰	195	27	13	b
Neonatal COS; n = 5					
Neonatal opioid withdrawal syndrome ⁴⁵	I = 0.54–28.6% of live births ⁴⁵	47	Not reported (Canada, UK, US, Europe)	13	a, b, d
Infant gastroesophageal reflux disease ⁴⁶	P ~ 100% (physiological in infants) ⁴⁷	264	>30	9	a, c, d
Infant colic ⁴⁸	P = 5–25% infants ⁴⁹	188	29	6	a, c, d
Neonatal research ²²	I = 10% of babies are admitted to neonatal unit ²²	414	25	12	a, b, d
Growth restriction in newborns ⁵⁰	I = 3–9% of pregnancies (developed world) ³⁶	53	2 (Netherlands & UK)	19	a, b, c, d
Pediatric (age < 8 years) COS; n = 15					
Otitis media with effusion (OME) in children with cleft palate ⁵¹	P = 0.14% of children have cleft palate, of whom 75% of have OME (0.11%) ⁵¹	147	1 (UK)	11	a, b, d
Protracted bacterial bronchitis ⁵²	P = 10% (Aboriginal children—Aus) ⁵³	36	1 (UK)	6	a, d
Rolandic epilepsy in childhood (as exemplar for childhood epilepsy) ⁴⁸	P = 0.16% (aged 0–19) ³⁰	102	1 (UK)	39	a, c, d
Peripheral vascular malformations ⁵⁴	P = 1% (venous malformations) ⁵⁵	301	Not reported (International)	17	a, c, d
Acute diarrhea ⁵⁶	I = 4000 episodes per 1000 children/year ⁵⁷	101	Not reported (Europe)	9	a, d
Childhood constipation ⁵⁸	P = 0.7–29.6% children ⁵⁸	433	28	8	a, c
Otitis media with effusion in otherwise healthy children <12 (ref. ⁵⁹)	P = 3.7–5.5% ³⁰	134	16	9	a, b
Infant feeding and prevention of childhood obesity ⁶⁰	P (Aus) = up to 20% overweight or obese ⁶⁰	253	35	26	a, b, d
Juvenile idiopathic arthritis ⁶¹	P = 0.4% ³⁰	190	50	5	a
Antiepileptic therapy in children ⁶²	P = 0.16% (aged 0–19) ³⁰	97	1 (Sri Lanka, with international involvement)	8	b, c

Table 1 continued

Condition	Incidence (I) or prevalence (P)	Number of stakeholders ^x	Number of countries	Number of core outcomes	Limitations
Uncomplicated appendicitis ⁶³	P = 0.125% of children ⁶⁴	147	1 (UK)	14	a, d
Pediatric functional abdominal pain disorders ⁶⁵	P = 13.5% worldwide ⁶⁵	305	International (including developing)	8	a
Pediatric critical care ⁶⁶	P = 1.5% of pediatric admissions ⁶⁷	206	Not reported (International)	8	c
Childhood asthma ⁶⁸	P = 11.0% (age 0–14 years) ³⁰	93	1 (UK)	4	a, c
Pediatric cardiac arrest ⁶⁹	I > 20,000 children per year (US) ⁶⁹	89	12	5	b, c
Adult COS (age 18–50 years); n = 14					
Polycystic ovarian syndrome ⁷⁰	P = 8–13% women of reproductive age ⁷⁰	194	17	33	b, d
Adult cardiac surgery ⁷¹	I (Aus) = 12,000 surgeries per year ⁷²	86	23	4	a
Type 1 diabetes in young adults (15–30) ⁷³	P = 0.3% ³⁰	132	15	8	a, d
Trials in hemodialysis ⁷⁴	Chronic kidney disease: P (Aus) ~ 10% adults ⁷⁵	1181	73	5	a
Type 2 diabetes mellitus ⁷⁶	P (45–49 years) = 3.6% ³⁰	173	14	18	a, b, d
Cardiac arrest ⁷⁷	I (Aus) = 33,000 people per year ⁷⁸	168	15	3	a, b
Chronic rhinosinusitis ⁷⁹	P = 11% adults ⁷⁹	110	Not reported (UK, Europe, Aus)	15	a, d
Cardiovascular outcomes in hemodialysis trials ⁸⁰	Chronic kidney disease: P (Aus) ~ 10% adults ⁷⁵	676	53	4	a
Shoulder disorders ⁸¹	P = 7–26% ⁸¹	335	13	4	a
Coronavirus disease 2019 (suspected or confirmed) ⁸²	N/A—ongoing pandemic	9289	111	6	e
Discharge from inpatient mental health services ⁸³	I (Aus) = 1.05% (overnight mental health admissions) ⁸⁴	104	12	4	a
Bipolar disorder ⁸⁵	P = 0.1–0.9% ³⁰	50	1 (UK)	11	a, c, d
Vascular access outcomes in hemodialysis ⁸⁶	Chronic kidney disease: P (Aus) ~ 10% adults ⁷⁵	873	58	12	e
Endometriosis ⁸⁷	P = 10–15% of women of reproductive age ⁸⁸	378	25	13	a

I incidence, P prevalence, UK United Kingdom, Aus Australia.

^x Maximum number of stakeholders involved in Delphi survey or consensus, i.e., number who participated in Round 1 of survey; not accounting for attrition.

a—Western/developed/high-income countries over-represented, or single country involved in development.

b—COS included long-term outcomes that may not be able to be recorded in all studies.

c—limited literature search for outcomes—pragmatic, not systematic review, proportionate systematic review, outcomes suggested by participants.

d—many and/or specific outcomes that may not be feasible for life course studies.

e—rapid methodology used (international survey to consensus workshops) without multiple rounds. However, lots of respondents and countries represented, so likely to still be a valid tool.

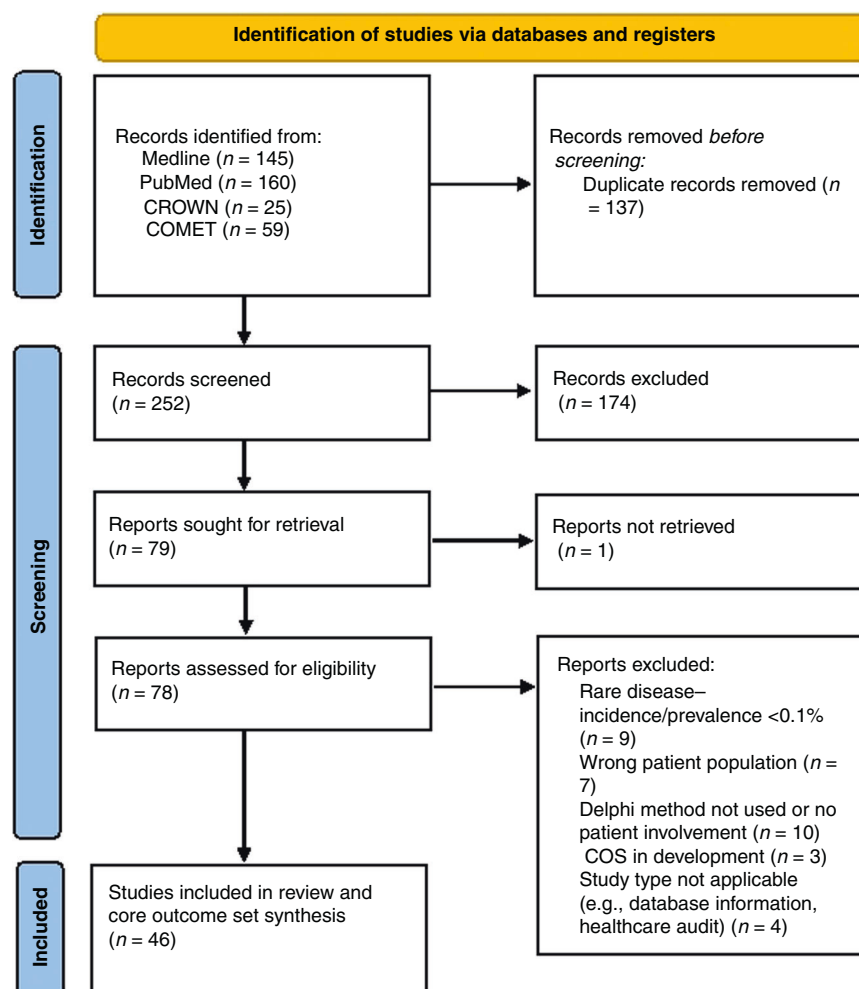


Fig. 1 PRISMA (2020) diagram. From Page et al.¹⁵. For more information, visit: <http://www.prisma-statement.org/>.

example, “activities of daily living” and “ability to perform normal activities” were termed “activities of daily living”; “spontaneous preterm labor”, “extremely preterm birth <28 weeks”, and “iatrogenic preterm birth” were all labeled “preterm birth”; and core outcomes relating to specific location or features of pain became the overarching construct “pain”.

Once synthesis was completed, we classified each overarching construct under one of the five taxonomic domains. A table displaying the individual core outcomes that were synthesized to produce each overarching construct is available as Supplementary Material 4.

RESULTS

Literature search

Database searches identified 145 articles in Medline, 160 in PubMed, 25 in CROWN, and 59 in COMET. After removing duplicates, we screened 252 records by title and abstract and excluded a further 174. The remaining 78 studies underwent full-text review for eligibility, and a final 46 COS studies were included in the core outcome mapping. This search strategy is displayed in a PRISMA diagram (see Fig. 1).

Of the included COS, 12 related to conditions of pre-pregnancy, pregnancy, or birth; 5 related to neonates; 15 were relevant to children <8 years old; and 14 addressed conditions affecting adults aged 18–50 years. Table 1 summarizes the characteristics of each COS, including study-specific limitations that could introduce bias.

Outcome synthesis

We identified a total of 414 unique core outcomes from 46 COS. We grouped these outcomes into 118 overarching constructs. We ordered the overarching constructs within the life stages by the total number of COS in which each outcome appeared, as shown in Table 2.

The overarching constructs relating to “quality of life”, “adverse events”, “hospitalization”, “medication/treatment use”, and “death/mortality” were the most common across all four life stages. These constructs align closely with four of the five domains from Dodd’s outcomes taxonomy utilized for our synthesis process, namely Life Impact, Adverse Events, Resource Use, and Death.²⁰ Meanwhile, the constructs in the Physiological and Clinical domain were more varied according to the diseases addressed by the COS relevant to that life stage. We note that COS that were excluded due to very low prevalence ($<0.1\%$) of conditions such as Hirschsprung’s disease²¹ often contained general (e.g., psychological distress, quality of life) as well as highly specific (e.g., need for a permanent stoma) core outcomes, supporting our belief that even rare conditions would show commonalities in the outcomes valued by stakeholders.

Pregnancy outcomes

In the pregnancy life stage, 34 overarching constructs were drawn from 14 COS (12 pregnancy COS, plus the adult endometriosis and polycystic ovarian syndrome, PCOS, COS). The two most frequently identified constructs were “fetal or neonatal loss” including miscarriage, termination of pregnancy or stillbirth, and “maternal

Table 2. Number of overarching constructs in each population by taxonomic domain.

	Pregnancy	n	Neonatal	n	Pediatric	n	Adult	n
Death	Fetal/pregnancy loss	9	Neonatal mortality	14	Mortality	4	Mortality	8
	Maternal mortality	7						
	Live birth	6						
Physiological & Clinical	Preterm birth	6	Birthweight (including low)	10	Pain	6	Cardiovascular health & morbidity	5
	Mode of birth	4	Gestational age at birth	7	Gastrointestinal morbidity	6	Neurological function/stroke	4
	Pre-eclampsia & its complications	4	Congenital anomalies	6	Breastfeeding	6	General health parameters	4
	Gestational diabetes (control & complications)	4	Neonatal morbidity	6	Growth & weight	5	Metabolic health	3
	Gestational weight gain	3	Small for gestational age	4	Hearing impairment	5	Control of disease	2
	Hemorrhage (intra/postpartum)	3	Neonatal infection/sepsis	4	Neurodevelopmental morbidity	4	Glycemic abnormalities & emergencies	2
	Hypertensive disorders of pregnancy	3	Neonatal seizures	4	Feeding problems & behavior	4	Kidney health	2
	Viable pregnancy	3	Neurological damage	4	Physical health	3	Respiratory morbidity	1
	Inflammation or infection	2	Neonatal hypoglycemia	2	Respiratory infection/morbidity	3	Multi-organ failure	1
	BMI	1	Large for gestational age	2	Infection	3	Gynecological health & morbidity	1
	Blood pressure	1	Length at birth	2	Visual impairment	3	Diabetic complications	1
	Thyroid function	1	Bloods & electrolytes	1	Symptom severity	3	Physical health	1
	Ectopic pregnancy	1	APGARs	1	Seizures	2	Disease prevention	1
	Prenatal & antenatal care	1	Head circumference at birth	1	Joint signs	1		
	Epilepsy & its complications	1			Breathing difficulties	1		
	Gastrointestinal morbidity	1			Formula/solids introduction	1		
	Hydration & electrolytes	1			Types of food consumed	1		
	Induction or augmentation of labor	1			Foods offered	1		
	Cardiovascular health	1			Eating behaviors & environment	1		
	Time to pregnancy leading to live birth	1			Developmental milestones	1		
	Pre-labor rupture of membranes (PROM)	1			Prevention & recovery	1		
Life impact	Quality of life (including HRQL)	3	Parental quality of life	2	Quality of life (child)	10	Quality of life	10
	Postnatal depression	3			Physical function & disability	8	Symptom/disease burden	8
	Medication compliance	3			Cognitive function & ability	5	Activities of daily living	4
	Patient satisfaction	3			Normal day-to-day activities	4	Psychological health	3
	Other mental health	3			Mental health & wellbeing	4	Patient-centered care	2
					Social development	4	Health literacy	1
					Speech & language	4	Health-related behavior	1
					Sleep quality, duration	3		
					Crying, Consolability	3		

Table 2 continued

	<i>n</i>	<i>n</i>	<i>n</i>	<i>n</i>	<i>n</i>
<i>Pregnancy</i>	<i>Neonatal</i>	<i>Pediatric</i>	<i>Adult</i>	<i>n</i>	<i>n</i>
		Satisfaction with treatment	3		
		School attendance/performance	3		
		Quality of family life	2		
		Patient perception of disease	2		
		Treatment compliance	1		
Adverse events	4	Harm from pregnancy or delivery intervention	3	12	Adverse events
	3	Complications—pregnancy, labor, postpartum			
	2	Uterine complications			
Resource use	6	Hospital or NICU admission, duration	7	4	Hospitalization and/or surgery
	5	Hospital or ICU admission	4	4	Treatment (compliance, duration, satisfaction)
		Respiratory support	3	1	
		Medical or surgical intervention			

n total number of COS in which the overarching construct appeared, *BMI* body mass index, *APGAR* appearance, pulse, grimace, activity, and respiration, *HRQL* health-related quality of life, *ADL* activities of daily living, *ICU* intensive care unit, *NICU* neonatal intensive care unit.

mortality". Other frequently identified constructs were "preterm birth", "medication or treatment required", "hospital or ICU admission", "live birth", "mode of delivery", "adverse effects from intervention", "pre-eclampsia and its complications", "gestational diabetes" and "other complications" of pregnancy, labor or the puerperium. In addition to quality of life, mental health was reflected in the constructs of "postnatal depression" and "other mental health".

Neonatal outcomes

For neonates, 20 overarching constructs were derived from 17 COS, which included pediatric, pregnancy, adult and a dedicated neonatology COS.²² The single most identified construct was "neonatal mortality". This was followed by "birthweight" including low birthweight, "hospitalization or NICU admission", and "gestational age at birth". Other common neonatal constructs, representing the Physiological and Clinical, Adverse Events, and Resource Use domains included "neonatal seizures", "small for gestational age", "neurological damage", "harm from delivery/pregnancy intervention", "neonatal morbidity", "neonatal infection/sepsis", "medical or surgical intervention", "congenital anomalies", "respiratory support", and "neonatal hypoglycemia".

Pediatric outcomes

For children <8 years old, 40 overarching constructs from 29 COS related both to pregnancy and pediatrics. The most common constructs were "adverse events" following either a condition or treatment and "quality of life". These were followed by "pain", "gastrointestinal morbidity", "hospitalization", "growth and weight", "neurodevelopmental morbidity", "physical function/disability", "mortality", "physical health", and "treatment failure/escalation". Furthermore, the Life Impact domain was represented by constructs such as "cognitive function/ability", "breastfeeding" encompassing maternal confidence and duration, "feeding problems/behavior", "school performance and attendance", "hearing", "speech and language", "mental health and wellbeing", "sleep quality and duration", and "social development". Other seldom-identified constructs that may be notable to life course studies were "quality of family life" and food-related constructs including "types of foods consumed", "foods offered", and "eating behaviors and environments".

Adult outcomes

From the 14 COS addressing adults aged 18–50 (the relevant age range for most parents of young children), we derived 24 overarching constructs. The most consistently identified constructs were "quality of life" (with "psychological health" in a further three COS) "symptoms & disease burden", and "mortality". The next tier encompassed "adverse events", "hospitalization and/or surgery", and "cardiovascular health/morbidity". Following this were "neurological function/stroke", "activities of daily living", and "general health parameters", such as body mass index (BMI).

DISCUSSION

Principal findings

From 46 published COS addressing pregnancy, newborns, children <8 years old, and younger adults (aged 18–50 years), we synthesized 118 overarching constructs from 414 unique core outcomes. The prioritized outcomes were typically broad, spanning all aspects of functioning—physical, mental, social, cognitive, participation—with commonalities across multiple COS even when the condition generating an individual COS was rare. The most common overarching constructs across all four life stages were "quality of life", "adverse events", "medication use", "hospitalization", and "mortality", which aligned with the taxonomic domains that guided our synthesis. We believe that our synthesis and methodology may be helpful to others in

prioritizing outcomes for early life course studies, especially those desiring interventional and strong causal reasoning capabilities.

Strengths

To our knowledge, this systematic approach to synthesizing COS is unique. We collated core outcomes from multiple published COS across the age ranges most relevant to new birth cohorts, and utilized a robust existing taxonomic framework from Dodd et al.²⁰ to guide our classification process. The identified constructs reflect widely prioritized outcomes across life stages most relevant to birth cohorts. Many of these constructs span the spectrum of good and poor health and well-being, are measurable, and could be modifiable with intervention. This emphasizes the importance of life course studies taking a holistic, strength-based approach to outcomes, rather than over-focusing on deficits—aneccdotally, a common complaint of participants. We clearly describe our synthesis process so it could be adapted to identify outcomes for other populations (e.g., adolescents, older adults). Beyond identifying outcomes for an individual cohort, the COS synthesis approach could assist life course studies to standardize outcomes with each other and with clinical trials to support harmonized meta-analysis and to triangulate causal inference.

Limitations

Despite the breadth of physical, mental, social, cognitive, and participation outcomes identified, the COS focus on outcomes relevant to trials in the health sector may undervalue or miss entirely some antecedents or outcomes important to observational life course research. For example, while our overarching constructs aligned with Dodd's taxonomy,²⁰ the latter additionally suggested some outcomes that appear important for consideration in life course studies (e.g., "Economic" and "Societal/Carer Burden" under the Resource Use domain.²⁰) Further, it is not known whether stakeholders would prioritize outcomes differently for life course research than for trials. Some fields are currently more active in COS research than others, including rheumatology,⁵ nephrology,²³ and women's and newborn health.¹⁹ This can result in certain constructs, such as the pediatric construct "*gastrointestinal morbidity*", appearing more frequently in the final list of constructs than morbidity in other organ systems; as more COS are completed, we expect this bias to reduce. Despite this bias, it was striking that our highly prioritized outcomes were overwhelmingly *not* condition-specific, again indicating the universality of the outcomes that children, parents, and services value most regardless of their individual challenges or conditions. A further source of bias is that COS often disproportionately involve stakeholders from English-speaking, high-income countries; while some constructs may therefore be missing, those we identified seem universal in their applicability.

Finally, there are some limitations relating to our methodology. COS typically specify *constructs* so that, even with this systematic methodology, choices of *scales* or *metrics* will still need to be made; however, we posit that harmonizing by construct is the critical first step towards harmonization by measure. As this was a rapid rather than a full systematic review, the methods were rigorous and well-documented, but it was not pre-registered and we did not undertake dual abstract screening or data extraction. Future work could also formalize criteria for synthesizing outcomes and assess their reliability.

Interpretation in the context of life course research

The population-specific overarching constructs we identified are also largely congruent with major morbidities and prominent causal theories for each life stage, which further supports their importance and inclusion in life course studies. For example, a common pregnancy construct was "preterm birth", which is associated with numerous perinatal, early childhood, and long-term adverse outcomes such as adult hypertension, hyperglycemia, and mental health

problems.²⁴ In newborns, the construct of "birthweight" reflects its importance in relation to key non-communicable health outcomes such as cardiovascular disease, diabetes, and obesity, as described by the Developmental Origins of Health and Disease (DOHaD) theory.²⁵ The overarching constructs for young children prioritized their development and participation, regardless of their medical condition(s), through constructs such as "growth and development", "school attendance/performance", and "social development". This is concordant with the work of Sinha et al.²⁶, which identified certain outcomes as particularly important for children, such as quality of life and functional status. Finally, the adult constructs, including "disease burden", "mental health", and "cardiovascular health/morbidity", reflect the impacts of classic life course diseases of ageing. For all of these issues, major gaps remain in understanding of causal pathways and effective interventions, suggesting that these measures synthesized by examining COS are highly relevant to life course cohorts.

Implications

Our approach of COS synthesis offers a transparent method of outcome selection for life course studies and provides a high-level list of constructs for consideration. This approach could help minimize selection bias, taking into account the views of very large numbers of stakeholders (children and families from many walks of life, multiple sectors and disciplines, diverse countries) with a depth and breadth not replicable in any one cohort. It could also help life course studies to better contribute to outcomes research across many fields, fulfilling the "collect once, use multiple times" paradigm. Capturing such outcomes over the long term could greatly extend the value of embedded trials or health services research, for which questions regarding lasting harms and benefits are typically out of reach due to short trial funding windows. This approach would also enable large multi-use life course cohorts to have an increased focus on causation and solutions than is typically possible through observational research alone.

We propose that life course studies could incorporate these highly prioritized domains and constructs into their process for selecting measures, supplementing it with other approaches to address the gaps in the current COS literature and ensure comprehensive and robust measurement. For example, GenV is also drawing from its life course frameworks¹ and consulting with stakeholders via methods including focus groups, an open focus area survey²⁷ and group prioritization activities with researchers.²⁸ Once a study has developed their outcome constructs, a standardized and reproducible measure must be identified for each. Given the generalizability-by-design of COS, we believe that this approach will allow life course studies like GenV to harmonize not only with other life course cohorts but with trials, registries, and health services research internationally.

Future research

Future life course studies might choose to use these findings, update this study with new COS, or reproduce its methodology for older children, adolescents, and/or ageing adults. Doing so would increase confidence that the most important constructs for different life stages are captured and that the cohort will support wide-ranging interventional as well as observational research. Future research could further explore outcome classification frameworks such as that by Dodd et al.²⁰ and also focus on developing population health COS to capture important outcomes relevant to the wider community, including outcomes (e.g., economic, carer burden) that are under-represented in COS but important to life course studies. Identifying such gaps could motivate the creation of COS in additional research areas, or prompt researchers to identify methods to supplement the COS synthesis approach for outcome selection. Finally, ongoing efforts by regulators, funders, researchers, and journals are required to

disseminate and utilize COS and ensure that agreed-upon stakeholder-driven outcomes are considered in all studies.

CONCLUSION

This COS synthesis generated a breadth of constructs relevant to birth cohort outcomes selection. Some constructs appeared in multiple COS spanning all four life stages examined (such as quality of life, hospitalization), while others appeared in multiple COS for individual life stages (such as pre-eclampsia, birthweight, social development, cardiovascular health/morbidity). The rigor and in-built stakeholder and trials perspectives of a COS-shaped outcomes selection approach could help position future cohorts to include life course interventions and stronger causal inferencing. This review's synthesized COS data are guiding outcome measures selection for the early years of a large new birth and parent cohort (GenV) and appear relevant to longitudinal population studies more generally.

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AUTHOR CONTRIBUTIONS

E.M., L.G., K.M., S.A. Clifford, S.A. Carter, and M.W. contributed to conception and design, acquisition of data, and/or analysis and interpretation of data; E.M., L.G., S.A. Clifford, and M.W. drafted the manuscript; all authors revised the manuscript critically for important intellectual content and approved the final version to be published.

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COMPETING INTERESTS

The authors declare no competing interests.

CONSENT STATEMENT

Patient consent was not required for this study.

ADDITIONAL INFORMATION

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