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Long-term economic return on investment for interventions in early childhood: Protocol for a systematic review

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Long-term economic return on investment for interventions in early childhood: Protocol for a systematic review

Geelhoed, E., Mandzufas, J., George, P., Strahan, K., Duffield, A., Borland, J., Li, I., Cross, D

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Abstract

Introduction:

Investment in early childhood produces positive returns: for the child, the family and the community. These returns have been shown to be significant within certain parameters, but a systematic review of evidence across multiple sectors including health, education and social welfare will have the capacity to provide information across a broader scope. The review will take a societal approach, encompassing all relevant costs and benefits to enable the identification of the most beneficial investments in early childhood and highlight gaps in current research.

Methods and analysis:

Economic evaluation studies which include both costs and outcomes of early childhood interventions and programs will be included. Outcomes may be valued in monetary units or quantified non-monetary units (e.g. quality adjusted life years, disability adjusted life years). Results will be expressed as a ratio according to the outcome; with monetary outcomes expressed as cost-benefit ratios or return on investment (ROI), and non-monetary outcomes expressed as cost per quality-adjusted life year (QALY) or disability-adjusted life year (DALY). The target population is children aged 0-5 years (from birth to school entry).

Databases for search will include MEDLINE, PsycINFO, EMBASE, National Health Service Economic Evaluation Database (NHS EED), Econ Lit, Paediatric Economic Database Evaluation (PEDE) and Education Resources Information Center (ERIC). Reference lists will be searched for further relevant articles. The review will involve five phases: defining the research question, identifying relevant studies, selecting studies, extracting and collating data, and summarising and reporting results.

Ethics and dissemination:

The findings of this review will inform policy makers and practitioners in public health, education, social welfare and primary care settings. Exemption from ethics approval was granted by the University of Western Australia Human Ethics Office (RA/4/20/5677).

Systematic review registration:

This protocol has been submitted for registration with PROSPERO, file number 145901 (currently being assessed for registration).

Article summary

Strengths and limitations of this study

- Holistic approach to review evidence of early childhood investment
- Identification of gaps in the literature
- Internationally based

Limitations

- Different methodological approaches according to discipline and/or sector
- Contrasting priorities for investment according to income level of country

Introduction

Evidence indicates that investment in early childhood generates positive returns, for the child, the family and the wider community [1-5]. This is particularly so for children who struggle to pursue their full potential, due to poor health [6-8], lack of opportunities to learn [1-5], and/or deprivation of care [9, 10]. While the return on investment in early childhood has been shown to be significant within certain parameters, to date there is limited evidence addressing investment across multiple sectors (including health, education and social welfare) [11].

Early childhood interventions benefit children in the short term through the development of resilience, improved cognitive skills, reduced school absenteeism and reduced risk of disease; and may generate positive long-term outcomes through better employment pathways [1, 2], improved health [3, 6-8] and reduced dependency on welfare (including social services, incarceration and juvenile justice) [12-14]. Ensuing benefits in adulthood include better opportunities for employment and higher income [2], reduced risk of teenage pregnancy and crime and improved health outcomes [1]. Investment in disadvantaged children also has the potential to reduce inequality [3, 5], and to improve national productivity and gross domestic product (GDP) [1, 2, 4]. Conversely the cost of failing to adequately support children has implications for the child and the community, and, through the social and economic implications of that failure, to the national economy [15].

Much of the research on successful early childhood interventions and programs supports the need to intervene prior to formal school entry. For instance, developmental neuroscience emphasises ages 0 to 5 years as the optimal time to intervene [3] based on the rate of change that occurs physically and mentally during this period. Interventions initiated between the ages of 0 and 3 years have been shown to yield the highest economic returns, particularly for children experiencing adversity [6]. Determining the optimal timing, duration and threshold of intensity of intervention is an important focus for this review.

While the benefit of early childhood investment is well-established per se, priorities for the best allocation of resources are less clear. Understanding the comparative 'value' of a program [5] is central to enabling policy choices. This 'value' can be expressed in terms of cost-effectiveness (the cost required to achieve a given outcome), as cost-benefit (the ratio of cost inputs to dollar benefits) or as Return on Investment (ROI), which compares net profit with cost inputs. Typically, health programs are valued according to costs per Quality Adjusted Life Year (QALY) or cost per Disability Adjusted Life Year (DALY) whereas in education, value is more typically presented in terms of cost-benefit or ROI.

Consistent with the World Health Organization (WHO) definition of health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [16], individual outcomes are specified broadly, encompassing a child's whole life potential. For example, optimal health for the young child includes the development of resilience and the opportunities to achieve throughout their life. Aggregation of individual outcomes provides economic outcomes at a community, national, and global level.

A systematic review of the peer-reviewed literature across all sectors will synthesise the economic evidence on interventions directed toward infants and children (those aged 0 to 5 years), for legislators, practitioners and policy makers. Health, education and welfare spending on young children is increasingly resource constrained and must compete with other demands. A comprehensive and clear summary of the evidence base is a prerequisite for a rational and justifiable prioritization of the wide range of options for investment in early childhood.

The aim of this study is to systematically review economic evidence on population interventions targeted at children aged 0-5 years across multiple sectors including health, education and social welfare to compare relative return on investment.

Methods and Analysis

Eligibility criteria

The review will include economic evaluation studies in peer-reviewed journals containing both costs and non-monetary outcomes (including cost-minimisation, cost-utility, cost-effectiveness) or costs and outcomes valued in monetary terms (cost-benefit and other return on investment). The sectoral differences in approach to economic evaluations, for example the use of cost-benefit analysis in the education sector and cost effectiveness in health, will be transparently addressed .Given the potential variation in methodological approach, it may be necessary to present economic ratios specific to each sector or within sub-groups such as vulnerable and low socioeconomic groups.

Participants in reviewed studies will primarily be infants and children aged 0 to 5 years; but may also include alternative groups such as parents, where outcomes relate to children. Studies including broader population age groups will be considered where data relating to 0 to 5 year-olds can be separately extracted.

Interventions may have broad scope including vaccination, nutrition and health management; early childhood learning, access to early childhood programs and the organisation of early learning; and the impact of poverty, maternal employment and parental incarceration. Only 'public health' interventions, encompassing investments in health, education and social welfare to optimise the potential of the whole person [16] will be included. Acute care or diagnostic choices in tertiary care will not be included.

Experimental and quasi-experimental studies will be included. All interventions will be assessed against a control, although the comparator may be 'no intervention'. Additional components of quality will be considered within a set template and studies may be excluded if they do not meet the agreed criteria. Only studies that involve both an investment in early childhood and a measured benefit will be reviewed. Studies will be excluded if costs unrelated to outcomes for young children are the primary outcome measure or if outcomes are not included in the publication.

Information sources

The following electronic databases will be searched: MEDLINE (Ovid), EMBASE (Ovid), PsycInfo (Ovid), National Health Service Economic Evaluation Database (NHS EED), Econ Lit, Paediatric Economic Database Evaluation (PEDE) and Education Resources Information Center (ERIC).

Reference lists of included studies will be hand searched to identify further papers. Authors of particularly germane studies may be contacted for additional pertinent material where considered necessary. References cited in relevant systematic reviews will be searched for additional eligible studies.

Search strategy

Indexing of the literature varies between the listed electronic databases, requiring tailored search specifications. For example, databases dedicated to predefined criteria, such as “paediatric”, do not require inclusion of that criterion in the search.

The search strategy to be applied to the Ovid platform (MEDLINE, EMBASE, PsycInfo) will be used in a modified form for all other databases. For example, in Medline the search will combine exp Child, Preschool/, INFANT/, early childhood.mp and (preschool child* or infant* or prekindergarten or kinder* or child*).mp. This will be specified as: all infant (birth to 23 months) or newborn infant (birth to 1 month) or infant (1 to 23 months) or preschool child (2 to 5 years). Cost-Benefit Analysis/, exp Quality-Adjusted Life Years/, (return on invest* or "cost and cost analysis" or economic evaluation or QALY or DALY or "quality adjusted life year*" or ROI or cost benefit*) will be combined.

The search in all databases will be limited to peer reviewed journals published since 2000; classified as journal article (ie no conference proceedings, supplements, or letters); and relating to human research.

Study records

Data management

Search results will be imported into Covidence [17] and automatically deduplicated. Additional duplicates will be manually identified and removed once full text comparison is undertaken.

Selection process

The CoLab Economics Systematic Review Consultancy Group comprises internationally recognised professional staff, consultants, and senior economists. This group provided advice on the design of the study and will be involved in other facets of the data collection and analysis.

Two reviewers will independently examine the titles and abstracts retrieved through the search process to identify studies that do not meet the stated eligibility criteria. At this level any economic evaluation measuring cost effectiveness, cost-utility or return on investment from interventions affecting the immediate and/or lifetime health, education, labour or social welfare outcomes of infants and children, other than clinical treatment outcomes, will be included. Lack of consensus between reviewers on study inclusion will be resolved through discussion. Where necessary a third reviewer will be consulted. Full texts of the remaining potentially relevant records will be retrieved in order to proceed to independent evaluation by two reviewers.

Data collection

An extraction template, using an adapted checklist, will be piloted and refined by staff, and circulated to the Consultancy group for further piloting, discussion and approval. Data items included in the extraction may be modified following piloting. At least two independent reviewers will extract data from the full text of selected studies. Extracted data will be compared and conflicts between the reviewers discussed and resolved.

Data items

The characteristics of included studies will be described based on the following:

I. General categorising information (sector information, category, condition, intervention, study question)

II. Country and income level (using World Bank classifications) [18]

III. Population characteristics and reason for selection (age group, stratification, target criteria, number of participants)

IV. Perspective of the economic evaluation (societal, government, etc.)

V. Time horizon

VI. Economic study type and outcome ratio

VII. Comparator(s) or base case and justification for comparator

VIII. Costing approach (currency, index year for costs, standardisation methods, cost components, cost sources, discount rate)

IX. Outcomes (measure of benefit in evaluation, discount rate applied in outcomes)

X. Sensitivity analyses (parameters, methods and results)

XI. Credibility and conflicts of interest (eg funder)

XII. Modelling (type, structure, assumptions, sources, cycle length and validation)

XIII. Feasibility/necessity to contact study authors to obtain missing information

XIV. Quality (subjective)

a. Research methods (PICO)

b. Risk of bias – selection, performance, detection, attrition, reporting

c. Imprecision - confidence intervals, sample size

d. Inconsistency

e. Publication bias

At the full text retrieval stage reviewers will examine the economic methods used, the useability of studies containing partially age relevant data and the significance of studies that require modelling inputs.

Risk of bias in individual studies

The quality of the selected studies will be transparently reported based on the economic evaluation methods used, validity of assumptions and possible inherent biases. Two independent reviewers will assess the certainty of evidence considering risk of bias, imprecision, inconsistency, indirectness and publication bias. Five sources of bias in reported outcomes will be assessed: selection, performance, detection, attrition and reporting. Study authors who are contactable may be requested to provide pertinent and available missing data.

For each included study, both reviewers will assess the risk of bias and assign ratings of low, high or unclear risk of bias. Disagreement will be resolved via discussion between the two reviewers until they reach consensus or through referral to an independent third reviewer. Final decisions will be recorded in a 'Risk of bias' table with a rationale for each decision.

Data

Synthesis

Results will be reported consistent with the PRISMA 2009 checklist.

In consideration of differing economic evaluation methodologies across sectors, a narrative synthesis of data will be undertaken. Narrative format 'Summary of Findings' (SoF) tables will present the key results of the

review, including ranking of the certainty of the evidence upon which these results are based. Tables will be developed according to the outcome variable, or the means of reporting returns on investment. Information on population, intervention, comparison, setting and certainty of evidence will also be reported.

Comparisons will be made within sector (eg health sector using QALYs) but also across sectors, requiring conversion to a common monetary unit. For the purposes of comparison, QALYs will be converted to Net Benefit, to monetise outcomes. This requires the assumption of a 'willingness to pay' threshold to convert QALYs to a common monetary unit.

Patient and public involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Discussion

This systematic review will be the first to consider cross-sector economic evaluation of investment in early childhood. Whilst this presents some methodological challenges, the results will provide invaluable information to assist ranking whole-of-government priorities and forming policy recommendations and identify gaps in current literature. This project demonstrates a global perspective, with national policy implications.

The lack of consistent outcome measures between important sectors represents a potential limitation of the review. For example, the conversion of outcomes to monetary units is contentious because of the assumptions required. Further benefits of early intervention may be difficult to quantify because they are intangible (e.g. resilience or self-belief) or because of extrapolation methods of predicting far into the future (e.g. adult employment). Furthermore, while the cost effectiveness and ROI of outcomes in the health, social welfare and education sectors can be measured or estimated, impacts on inequality, intergenerational

outcomes and benefits at a societal level may be less easily quantified. Such limitations will be addressed transparently and as subgroups where necessary.

Summary evidence will provide policy makers with cross-sectoral information relevant to strategic decision-making for early childhood investment.

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Authors' contributions

Elizabeth Geelhoed led the protocol drafting and is the guarantor of the review. Other authors contributed to reviews of further drafts and study methodology discussions.

Funding

This work was supported by CoLab - Collaborate for Kids, a partnership between the Telethon Kids Institute and the Minderoo Foundation, made possible with funding from the Minderoo Foundation. Staff and external consultants are contracted by CoLab.

The funders had no input to the design of the study or development of the protocol.

Competing interests

None declared.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	5
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	NA
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	NA
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	NA
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	NA
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	NA
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Abstract

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Economic evaluations which incorporate both costs and long-term outcomes of early childhood interventions and programs will be included. Outcomes may be valued in monetary units or quantified non-monetary units (e.g. quality adjusted life years, disability adjusted life years). Results will be expressed as a ratio according to the outcome; with monetary outcomes expressed as cost-benefit ratios or return on investment (ROI), and non-monetary outcomes expressed as cost per quality-adjusted life year (QALY) or disability-adjusted life year (DALY). The target population is children aged 0-5 years (from birth to school entry).

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Introduction

Evidence indicates that investment in early childhood generates positive returns, for the child, the family and the wider community [1-5]. Benefits to children in the short term include the development of resilience, improved cognitive skills, reduced school absenteeism and reduced risk of disease. Longer term outcomes include better employment pathways [1, 2], improved health [3, 6-8] reduced dependency on welfare (including social services, incarceration and juvenile justice) [9-11] and reduction in inequality [3, 5]. This is particularly so for children who struggle to pursue their full potential, due to poor health [6-8], lack of opportunities to learn [1-5], and/or deprivation of care [12, 13]. Ultimately these benefits have implications for improving national productivity and gross domestic product (GDP) [1, 2, 5]. Conversely the cost of failing to adequately support children has implications for the child and the community, and, through the social and economic implications of that failure, to the national economy [14]. While the benefits of investment in early childhood have been shown to be significant within certain parameters, to date there is limited evidence addressing investment across multiple sectors (including health, education and social welfare) [15].

Much of the research on successful early childhood interventions and programs supports the need to intervene prior to formal school entry. For instance, developmental neuroscience emphasises ages 0 to 5 years as the optimal time to intervene [3] based on the rate of change that occurs physically and mentally during this period. Interventions initiated between the ages of 0 and 3 years have been shown to yield the highest economic returns, particularly for children experiencing adversity [6].

While the benefit of early childhood investment is well-established per se, priorities for the best allocation of resources are less clear. Understanding the comparative 'value' of a program [5] is central to enabling policy choices. This 'value' can be expressed in terms of cost-effectiveness (the cost required to achieve a given outcome), as cost-benefit (the ratio of cost inputs to dollar benefits) or as Return on Investment (ROI), which compares net profit with cost inputs. Typically, health programs are valued according to cost per Quality

Adjusted Life Year (QALY) or cost per Disability Adjusted Life Year (DALY) whereas in education, value is more typically presented in terms of cost-benefit or ROI.

Consistent with the World Health Organization (WHO) definition of health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [16], individual outcomes are specified broadly, encompassing a child's whole life potential. For example, optimal health for the young child includes the development of resilience and the opportunities to achieve throughout their life.

A systematic review of the peer-reviewed literature across all sectors will synthesise the economic evidence on interventions directed toward infants and children (those aged 0 to 5 years), for legislators, practitioners and policy makers. Given the complementarity of interventions a systematic review of evidence that is not siloed by sector has the capacity to broadly address the range of social determinants.

The aim of this study is to systematically review economic evidence on population interventions targeted at children aged 0-5 years across multiple sectors including health, education and social welfare.

Methods and Analysis

Eligibility criteria

The review will include economic evaluation studies in peer-reviewed journals containing both costs and non-monetary outcomes (including cost-minimisation, cost-utility, cost-effectiveness) or costs and outcomes valued in monetary terms (cost-benefit and other return on investment). The sectoral differences in approach to economic evaluations, for example the use of cost-benefit analysis in the education sector and cost effectiveness in health, will be transparently addressed. Given the potential variation in methodological approach, we will present economic ratios specific to each sector or within sub-groups such as vulnerable and low socioeconomic groups.

Participants will primarily be infants and children aged 0 to 5 years; but may also include alternative groups such as parents, where outcomes relate to children. Studies including broader population age groups will be reviewed where data relating to 0 to 5 year-olds can be separately extracted.

Interventions may have broad scope including vaccination, nutrition and health management; early childhood learning, access to early childhood programs and the organisation of early learning; and the impact of poverty, maternal employment and parental incarceration. Acute care or diagnostic choices in tertiary care will not be included.

All interventions will be assessed against a control, although the comparator may be 'no intervention'. Additional components of quality will be assessed within a set template and studies may be excluded if they do not meet the agreed criteria. Only studies that involve both an investment in early childhood and a measured benefit will be reviewed. Studies will be excluded if they do not report both costs (inputs) and benefits (outputs). Full inclusion and exclusion criteria are listed in Table 1.

Table 1

Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Economic evaluations with investment in early childhood and measured long-term benefit	No outcomes quantified
Peer reviewed journal articles	Supplements, letters, conference abstracts and proceedings
Participants: children aged 0-5 years and others (e.g. parents where outcomes relate to children aged 0-5 years)	No separate extraction for 0-5 years possible

	Published prior to 2000 Interventions of acute care, treatment, diagnostic choices

Information sources

Following advice from generalist and specialist librarians (health and medical, business and economics), the following electronic databases have been identified as information sources: MEDLINE (Ovid), EMBASE (Ovid), PsycInfo (Ovid), National Health Service Economic Evaluation Database (NHS EED), Econ Lit, Paediatric Economic Database Evaluation (PEDE) and Education Resources Information Center (ERIC).

Reference lists of included studies will be hand searched to identify further papers. Authors of particularly germane studies may be contacted for additional pertinent material where considered necessary. References cited in relevant systematic reviews will be searched for additional eligible studies.

Search strategy

To account for indexing variation between electronic databases, tailored search specifications have been developed for each database. For example, databases dedicated to predefined criteria, such as “paediatric”, do not require inclusion of that criterion in the search. The search strategy to be applied to the Ovid platform (MEDLINE, EMBASE, PsycInfo) will be used in a modified form for all other databases. For example, in Medline the search will combine exp Child, Preschool/, INFANT/, early childhood.mp and (preschool child* or infant* or prekindergarten or kinder* or child*).mp. This will be specified as: all infant (birth to 23 months) or newborn infant (birth to 1 month) or infant (1 to 23 months) or preschool child (2 to 5 years). Cost-Benefit Analysis/, exp Quality-Adjusted Life Years/, (return on invest* or "cost and cost analysis" or economic evaluation or QALY or DALY or "quality adjusted life year*" or ROI or cost benefit*) will be combined.

The search in all databases will be limited to peer reviewed journals published since 2000; classified as journal article (i.e., no conference proceedings, supplements, or letters); and relating to human research. There will be no limitation on language of publication.

Study records

Data management

Search results will be imported into Covidence [17] and automatically deduplicated. Additional duplicates will be manually identified and removed once full text comparison is undertaken.

Selection process

The CoLab Economics Systematic Review Consultancy Group comprises internationally recognised professional staff, consultants, and senior economists. This group provided advice on the design of the study and will be involved in other facets of the data collection and analysis.

Two reviewers will independently examine the titles and abstracts retrieved through the search process to identify studies that do not meet the stated eligibility criteria. At this level any economic evaluation measuring cost effectiveness, cost-utility or return on investment from interventions affecting the immediate and/or lifetime health, education, labour or social welfare outcomes of infants and children, other than clinical treatment outcomes, will be included. Lack of consensus between reviewers on study inclusion will be resolved through discussion. Where necessary a third reviewer will be consulted. Full texts of the remaining potentially relevant records will be retrieved in order to proceed to independent evaluation by two reviewers.

Data collection

An extraction template, using an adapted checklist, will be piloted and refined by staff, and circulated to the Consultancy group for further piloting, discussion and approval. Data items included in the extraction may be

modified following piloting. At least two independent reviewers will extract data from the full text of selected studies. Extracted data will be compared and conflicts between the reviewers discussed and resolved.

Data items

The characteristics of included studies will be described based on the following:

I. General categorising information (sector information, category, condition, intervention, study question)

II. Country and income level (using World Bank classifications) [18]

III. Population characteristics and reason for selection (age group, stratification, target criteria, number of participants)

IV. Perspective of the economic evaluation (societal, government, etc.)

V. Time horizon

VI. Economic study type and outcome ratio

VII. Comparator(s) or base case and justification for comparator

VIII. Costing approach (currency, index year for costs, standardisation methods, cost components, cost sources, discount rate)

IX. Outcomes (measure of benefit in evaluation, discount rate applied in outcomes)

X. Sensitivity analyses (parameters, methods and results)

XI. Credibility and conflicts of interest (e.g. funder)

XII. Modelling (type, structure, assumptions, sources, cycle length and validation)

XIII. Feasibility/necessity to contact study authors to obtain missing information

XIV. Quality (subjective)

a. Research methods (PICO)

b. Risk of bias – selection, performance, detection, attrition, reporting

c. Imprecision - confidence intervals, sample size

d. Inconsistency

e. Publication bias

At the full text retrieval stage reviewers will examine the economic methods used, the useability of studies containing partially age relevant data and the significance of studies that require modelling inputs.

Risk of bias in individual studies

The quality of the selected studies will be transparently reported based on the economic evaluation methods used, validity of assumptions and possible inherent biases. Two independent reviewers will assess the certainty of evidence considering risk of bias, imprecision, inconsistency, indirectness and publication bias. Five sources of bias in reported outcomes will be assessed: selection, performance, detection, attrition and reporting. Study authors who are contactable may be requested to provide pertinent and available missing data.

For each included study, both reviewers will assess the risk of bias and assign ratings of low, high or unclear risk of bias. Disagreement will be resolved via discussion between the two reviewers until they reach consensus or through referral to an independent third reviewer. Final decisions will be recorded in a 'Risk of bias' table with a rationale for each decision.

Data

Synthesis

Results will be reported consistent with the PRISMA 2009 checklist; a PRISMA diagram and checklist will be included at the completion of the review.

In consideration of differing economic evaluation methodologies across sectors, a narrative synthesis of data will be undertaken. Narrative format 'Summary of Findings' (SoF) tables will present the key results of the review, including ranking of the certainty of the evidence upon which these results are based. Tables will be developed according to the outcome variable, or the means of reporting returns on investment. Information on population, intervention, comparison, setting and certainty of evidence will also be reported.

Primary comparisons will be made within sector (e.g. health sector using QALYs). Secondarily, cross sectoral comparisons will be explored using willingness-to-pay thresholds to convert health outcomes to monetary units.

Patient and public involvement

This research will be done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Discussion

This systematic review will be the first to consider cross-sector economic evaluation of investment in early childhood. Whilst this presents some methodological challenges, the results will provide invaluable information to assist in ranking whole-of-government priorities and forming policy recommendations. The project reflects a global perspective, with national policy implications.

The lack of consistent outcome measures between sectors represents a potential limitation of the review in comparing cost-effectiveness. For example, the conversion of outcomes to monetary units is contentious because of the assumptions required. Furthermore, benefits of early childhood intervention may be difficult to quantify because they are intangible (e.g. resilience or self-belief) or because of extrapolation methods of predicting far into the future (e.g. adult employment). Moreover, while the cost effectiveness and ROI of outcomes in the health, social welfare and education sectors can be measured or estimated, impacts on inequality, intergenerational outcomes and benefits at a societal level may be less easily quantified. Such limitations will be addressed transparently and within subgroups where necessary.

Summary evidence will identify gaps in the literature and provide policy makers with cross-sectoral information relevant to strategic decision-making for early childhood investment.

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Authors' contributions

Elizabeth Geelhoed (EG) led the conception and design of the study protocol and drafting the paper, and is the guarantor of the review.

Joelie Mandzufas (JM) contributed to the design of the study protocol and critical revision of drafts.

Phoebe George (PG) contributed to the design of the study protocol and critical revision of drafts.

Kenneth Strahan (KS) contributed to the design of the study protocol and critical revision of drafts.

Alison Duffield (AD) contributed to the design of the study protocol and critical revision of drafts.

Ian Li (IL) contributed to the conception and design of the study protocol and critical revision of drafts.

Donna Cross (DC) contributed to the conception and design of the study protocol and critical revision of drafts.

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The funders had no input to the design of the study or development of the protocol.

Competing interests

None declared.

Medline(Ovid)

1. exp Child, Preschool/
2. INFANT/
3. early childhood.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4. (preschool child* or infant* or prekindergarten or kinder* or child*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
5. 1 or 2 or 3 or 4
6. exp Cost-Benefit Analysis/
7. exp Quality-Adjusted Life Years/
8. (return on invest* or "cost and cost analysis" or economic evaluation or QALY or DALY or "quality adjusted life year*" or ROI or cost benefit*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
9. 6 or 7 or 8
10. 5 and 9
11. ("cost" or "costs").tw.
12. 10 and 11
13. limit 12 to yr="2000 -Current"
14. limit 13 to journal article
15. limit 14 to humans
16. limit 15 to ("all infant (birth to 23 months)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)")

Embase(Ovid)

1. exp Child, Preschool/
2. INFANT/
3. early childhood.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4. (preschool child* or infant* or prekindergarten or kinder* or child*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
5. 1 or 2 or 3 or 4
6. exp Cost-Benefit Analysis/
7. exp Quality-Adjusted Life Years/
8. (return on invest* or "cost and cost analysis" or economic evaluation or QALY or DALY or "quality adjusted life year*" or ROI or cost benefit*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
9. 6 or 7 or 8
10. 5 and 9
11. ("cost" or "costs").tw.
12. 10 and 11

13. limit 12 to yr="2000 -Current"
14. limit 13 to journal
15. limit 14 to human
16. limit 15 to (infant or preschool child <1 to 6 years>)

Psycinfo(Ovid)

1. early childhood.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
2. (preschool child* or infant* or prekindergarten or kinder* or child*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
3. 1 or 2
4. (return on invest* or "cost and cost analysis" or economic evaluation or QALY or DALY or "quality adjusted life year*" or ROI or cost benefit*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
5. 3 and 4
6. cost.mp. or costs.tw. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
7. 5 and 6
8. limit 7 to yr="2000 -Current"
9. limit 8 to peer reviewed journal
10. limit 9 to human
11. limit 10 to (100 childhood or 120 neonatal or 140 infancy <2 to 23 mo> or 160 preschool age)

Eric(ProQuest)

1.	Ab (early childhood or infant* or toddler* or child*) AND ab(cost*)
2.	Filter(2000-current date)
3.	Filter (Peer reviewed)
4.	Filter(scholarly journal articles)
5.	Filter(Early Childhood Education or Kindergarten or Preschool education)

EconLit(EBSCO)

S8	(AB child* OR AB (infant or infants) OR AB (baby or babies) OR AB (preschool or kindergarten or "early childhood education") OR AB newborn) AND (S4 AND S7) **Expanders** - Apply related words **Search modes** - Boolean/Phrase
S7	AB child* OR AB (infant or infants) OR AB (baby or babies) OR AB (preschool or kindergarten or "early childhood education") OR AB newborn **Limiters** - Scholarly (Peer Reviewed) Journals; Published Date: 20000101-20191231 **Expanders** - Apply related words **Search modes** - Boolean/Phrase
S6	AB child* OR AB (infant or infants) OR AB (baby or babies) OR AB (preschool or kindergarten or "early childhood education") OR AB newborn **Limiters** - Scholarly (Peer Reviewed) Journals **Expanders** - Apply related words **Search modes** - Boolean/Phrase

S5	AB child* OR AB (infant or infants) OR AB (baby or babies) OR AB (preschool or kindergarten or "early childhood education") OR AB newborn **Expanders** - Apply related words **Search modes** - Boolean/Phrase
S4	AB ("cost benefit analysis" or "cost-benefit analysis" or "cost effective analysis") OR AB ("economic outcomes" or "economic evaluation" or "cost effectiveness") OR AB cost analysis OR AB economic analysis OR "cost utility" **Limiters** - Scholarly (Peer Reviewed) Journals; Published Date: 20000101-20191231 **Expanders** - Apply related words **Search modes** - Boolean/Phrase
S3	AB ("cost benefit analysis" or "cost-benefit analysis" or "cost effective analysis") OR AB ("economic outcomes" or "economic evaluation" or "cost effectiveness") OR AB cost analysis OR AB economic analysis OR "cost utility" **Limiters** - Published Date: 20000101-20191231 **Expanders** - Apply related words **Search modes** - Boolean/Phrase
S2	AB ("cost benefit analysis" or "cost-benefit analysis" or "cost effective analysis") OR AB ("economic outcomes" or "economic evaluation" or "cost effectiveness") OR AB cost analysis OR AB economic analysis OR "cost utility" **Expanders** - Apply related words **Search modes** - Boolean/Phrase
S1	AB ("cost benefit analysis" or "cost-benefit analysis" or "cost effective analysis") OR AB ("economic outcomes" or "economic evaluation" or "cost effectiveness") OR AB cost analysis OR AB economic analysis OR "cost utility" **Expanders** - Apply related words **Search modes** - Boolean/Phrase

PEDE(SickKids)

The PEDE database will only show less than 300 articles at a time, if more it will cause you to refine your search. Therefore for this database by limiting the years searched

TITLE_ABSTRACT child* and TITLE_ABSTRACT cost* Limiters: neonates (0-1month, infants (1 month to 1 year) child 1-12 2000-2017 **1401 records, more than 300 please refine your search**
TITLE_ABSTRACT child* and TITLE_ABSTRACT cost* Limiters: neonates (0-1month, infants (1 month to 1 year) child 1-12 Limited: 2000-03
TITLE_ABSTRACT child* and TITLE_ABSTRACT cost* Limiters: neonates (0-1month, infants (1 month to 1 year) child 1-12 Limited:2004-05
TITLE_ABSTRACT child* and TITLE_ABSTRACT cost* Limiters: neonates (0-1month, infants (1 month to 1 year) child 1-12 Limited 2006-07
TITLE_ABSTRACT child* and TITLE_ABSTRACT cost* Limiters: neonates (0-1month, infants (1 month to 1 year) child 1-12 Limited 2007-10
TITLE_ABSTRACT child* and TITLE_ABSTRACT cost* Limiters: neonates (0-1month, infants (1 month to 1 year) child 1-12 Limited 2010-13
TITLE_ABSTRACT child* and TITLE_ABSTRACT cost*

Limiters: neonates (0-1month, infants (1 month to 1 year) child 1-12 Limited 2014-16
TITLE_ABSTRACT child* and TITLE_ABSTRACT cost* Limiters: neonates (0-1month, infants (1 month to 1 year) child 1-12 Limited 2017

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	4
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	60
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	10-30
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	287-298
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	299-302
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	300-302
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	303
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	72-103
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	104-105
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	108-129
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	131-138
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	139-152
STUDY RECORDS					

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	153-156
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	157-168
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	169-174
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	175-200
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	175-200
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	201-211
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	222-224
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐	☒	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐	☒	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	217-224
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	217-219
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	217-219

BMJ Open

Long-term economic outcomes for interventions in early childhood: Protocol for a systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-036647.R2
Article Type:	Protocol
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Primary Subject Heading:	Public health
Secondary Subject Heading:	Health economics, Paediatrics
Keywords:	HEALTH ECONOMICS, PUBLIC HEALTH, Community child health < PAEDIATRICS, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Long term economic outcomes for interventions in early childhood: protocol for a systematic review

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Word count: 2099 words

Abstract

Introduction:

Investment in early childhood produces positive returns: for the child, the family and the community. Benefits have been shown to be significant within certain parameters, but a systematic review of the economic evidence across multiple sectors including health, education and social welfare will have the capacity to inform policy relative to the full range of social determinants. This review will take a broad approach, encompassing a range of costs and benefits to enable the identification of the most beneficial investments in early childhood and to highlight gaps in current research.

Methods and analysis:

Economic evaluations incorporating both costs and long-term outcomes of early childhood interventions and programs will be included. Outcomes may be valued in monetary units or quantified non-monetary units (e.g. quality adjusted life years, disability adjusted life years). Results will be expressed as a ratio according to the outcome; with monetary outcomes expressed as cost-benefit ratios or return on investment (ROI), and non-monetary outcomes expressed as cost per quality-adjusted life year (QALY) or disability-adjusted life year (DALY). The target population is children aged 0-5 years.

Extensive database searches across sectors will be undertaken. The review will involve five phases: defining the research question, identifying relevant studies, selecting studies, extracting and collating data, and summarising and reporting results. The search commenced in 2019 and the expected end date is December 2020.

Ethics and dissemination:

The findings of this review will inform policy makers and practitioners in public health, education, social welfare and primary care settings. The publication plan includes a series of academic publications, and policy

papers prepared and disseminated through Telethon Kids Institute networks. Exemption from ethics approval was granted by the University of Western Australia Human Ethics Office (RA/4/20/5677).

Systematic review registration:

This protocol has been registered with PROSPERO: Registration number CRD42020145901.

Article summary

Strengths and limitations of this study

- Holistic approach to review evidence of early childhood investment
- Identification of gaps in the literature
- Internationally based

Limitations

- Different methodological approaches according to discipline and/or sector
- Contrasting priorities for investment according to income level of country

Introduction

Evidence indicates that investment in early childhood generates positive returns, for the child, the family and the wider community [1-5]. Benefits to children in the short term include the development of resilience, improved cognitive skills, reduced school absenteeism and reduced risk of disease. Longer term outcomes include better employment pathways [1, 2], improved health [3, 6-8] reduced dependency on welfare (including social services, incarceration and juvenile justice) [9-11] and reduction in inequality [3, 5]. This is particularly so for children who struggle to pursue their full potential, due to poor health [6-8], lack of opportunities to learn [1-5], and/or deprivation of care [12, 13]. Ultimately these benefits have implications for improving national productivity and gross domestic product (GDP) [1, 2, 5]. Conversely the cost of failing to adequately support children has implications for the child and the community, and, through the social and economic implications of that failure, to the national economy [14]. While the benefits of investment in early childhood have been shown to be significant within certain parameters, to date there is limited evidence addressing investment across multiple sectors (including health, education and social welfare) [15].

Much of the research on successful early childhood interventions and programs supports the need to intervene prior to formal school entry. For instance, developmental neuroscience emphasises ages 0 to 5 years as the optimal time to intervene [3] based on the rate of change that occurs physically and mentally during this period. Interventions initiated between the ages of 0 and 3 years have been shown to yield the highest economic returns, particularly for children experiencing adversity [6].

While the benefit of early childhood investment is well-established per se, priorities for the best allocation of resources are less clear. Understanding the comparative 'value' of a program [5] is central to enabling policy choices. This 'value' can be expressed in terms of cost-effectiveness (the cost required to achieve a given outcome), as cost-benefit (the ratio of cost inputs to dollar benefits) or as Return on Investment (ROI), which compares net profit with cost inputs. Typically, health programs are valued according to cost per Quality

Adjusted Life Year (QALY) or cost per Disability Adjusted Life Year (DALY) whereas in education, value is more typically presented in terms of cost-benefit or ROI.

Consistent with the World Health Organization (WHO) definition of health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [16], individual outcomes are specified broadly, encompassing a child's whole life potential. For example, optimal health for the young child includes the development of resilience and the opportunities to achieve throughout their life.

A systematic review of the peer-reviewed literature across all sectors will synthesise the economic evidence on interventions directed toward infants and children (those aged 0 to 5 years), for legislators, practitioners and policy makers. Given the complementarity of interventions a systematic review of evidence that is not siloed by sector has the capacity to broadly address the range of social determinants.

The aim of this study is to systematically review economic evidence on population interventions targeted at children aged 0-5 years across multiple sectors including health, education and social welfare.

Methods and Analysis

Eligibility criteria

The review will include economic evaluation studies in peer-reviewed journals containing both costs and non-monetary outcomes (including cost-minimisation, cost-utility, cost-effectiveness) or costs and outcomes valued in monetary terms (cost-benefit and other return on investment). The sectoral differences in approach to economic evaluations, for example the use of cost-benefit analysis in the education sector and cost effectiveness in health, will be transparently addressed. Given the potential variation in methodological approach, we will present economic ratios specific to each sector or within sub-groups such as vulnerable and low socioeconomic groups.

Participants will primarily be infants and children aged 0 to 5 years; but may also include alternative groups such as parents, where outcomes relate to children. Studies including broader population age groups will be reviewed where data relating to 0 to 5 year-olds can be separately extracted.

Interventions may have broad scope including vaccination, nutrition and health management; early childhood learning, access to early childhood programs and the organisation of early learning; and the impact of poverty, maternal employment and parental incarceration. Acute care or diagnostic choices in tertiary care will not be included.

All interventions will be assessed against a control, although the comparator may be 'no intervention'. Additional components of quality will be assessed within a set template and studies may be excluded if they do not meet the agreed criteria. Only studies that involve both an investment in early childhood and a measured benefit will be reviewed. Studies will be excluded if they do not report both costs (inputs) and benefits (outputs). Full inclusion and exclusion criteria are listed in Table 1.

Table 1

Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Economic evaluations with investment in early childhood and measured long-term benefit	No outcomes quantified
Peer reviewed journal articles	Supplements, letters, conference abstracts and proceedings
Participants: children aged 0-5 years and others (e.g. parents where outcomes relate to children aged 0-5 years)	No separate extraction for 0-5 years possible

	Published prior to 2000 Interventions of acute care, treatment, diagnostic choices

Information sources

Following advice from generalist and specialist librarians (health and medical, business and economics), the following electronic databases have been identified as information sources: MEDLINE (Ovid), EMBASE (Ovid), PsycInfo (Ovid), National Health Service Economic Evaluation Database (NHS EED), Econ Lit, Paediatric Economic Database Evaluation (PEDE) and Education Resources Information Center (ERIC).

Reference lists of included studies will be hand searched to identify further papers. Authors of particularly germane studies may be contacted for additional pertinent material where considered necessary. References cited in relevant systematic reviews will be searched for additional eligible studies.

Search strategy

To account for indexing variation between electronic databases, tailored search specifications have been developed for each database. For example, databases dedicated to predefined criteria, such as “paediatric”, do not require inclusion of that criterion in the search. The search strategy to be applied to the Ovid platform (MEDLINE, EMBASE, PsycInfo) will be used in a modified form for all other databases. For example, in Medline the search will combine exp Child, Preschool/, INFANT/, early childhood.mp and (preschool child* or infant* or prekindergarten or kinder* or child*).mp. This will be specified as: all infant (birth to 23 months) or newborn infant (birth to 1 month) or infant (1 to 23 months) or preschool child (2 to 5 years). Cost-Benefit Analysis/, exp Quality-Adjusted Life Years/, (return on invest* or "cost and cost analysis" or economic evaluation or QALY or DALY or "quality adjusted life year*" or ROI or cost benefit*) will be combined. The complete search strategy is published as supplementary information.

The search in all databases will be limited to peer reviewed journals published since 2000; classified as journal article (i.e., no conference proceedings, supplements, or letters); and relating to human research. There will be no limitation on language of publication.

Study records

Data management

Search results will be imported into Covidence [17] and automatically deduplicated. Additional duplicates will be manually identified and removed once full text comparison is undertaken.

Selection process

The CoLab Economics Systematic Review Consultancy Group comprises internationally recognised professional staff, consultants, and senior economists. This group provided advice on the design of the study and will be involved in other facets of the data collection and analysis.

Two reviewers will independently examine the titles and abstracts retrieved through the search process to identify studies that do not meet the stated eligibility criteria. At this level any economic evaluation measuring cost effectiveness, cost-utility or return on investment from interventions affecting the immediate and/or lifetime health, education, labour or social welfare outcomes of infants and children, other than clinical treatment outcomes, will be included. Lack of consensus between reviewers on study inclusion will be resolved through discussion. Where necessary a third reviewer will be consulted. Full texts of the remaining potentially relevant records will be retrieved in order to proceed to independent evaluation by two reviewers.

Data collection

An extraction template, using an adapted checklist, will be piloted and refined by staff, and circulated to the Consultancy group for further piloting, discussion and approval. Standard checklists will be considered and

compared throughout the process. Data items included in the extraction may be modified following piloting. At least two independent reviewers will extract data from the full text of selected studies. Extracted data will be compared and conflicts between the reviewers discussed and resolved.

Data items

The characteristics of included studies will be described based on the following:

I. General categorising information (sector information, category, condition, intervention, study question)

II. Country and income level (using World Bank classifications) [18]

III. Population characteristics and reason for selection (age group, stratification, target criteria, number of participants)

IV. Perspective of the economic evaluation (societal, government, etc.)

V. Time horizon

VI. Economic study type and outcome ratio

VII. Comparator(s) or base case and justification for comparator

VIII. Costing approach (currency, index year for costs, standardisation methods, cost components, cost sources, discount rate)

IX. Outcomes (measure of benefit in evaluation, discount rate applied in outcomes)

X. Sensitivity analyses (parameters, methods and results)

XI. Credibility and conflicts of interest (e.g. funder)

XII. Modelling (type, structure, assumptions, sources, cycle length and validation)

XIII. Feasibility/necessity to contact study authors to obtain missing information

XIV. Quality (subjective)

a. Research methods (PICO)

b. Risk of bias – selection, performance, detection, attrition, reporting

c. Imprecision - confidence intervals, sample size

d. Inconsistency

e. Publication bias

At the full text retrieval stage reviewers will examine the economic methods used, the useability of studies containing partially age relevant data and the significance of studies that require modelling inputs. The breadth of the interventions suggests that an extensive discussion will be required to consider the value of literature where methods have not strictly complied with standard methodologies.

Risk of bias in individual studies

The quality of the selected studies will be transparently reported based on the economic evaluation methods used, validity of assumptions and possible inherent biases. Two independent reviewers will assess the certainty of evidence considering risk of bias, imprecision, inconsistency, indirectness and publication bias. Five sources of bias in reported outcomes will be assessed: selection, performance, detection, attrition and reporting. Study authors who are contactable may be requested to provide pertinent and available missing data.

For each included study, both reviewers will assess the risk of bias and assign ratings of low, high or unclear risk of bias. Disagreement will be resolved via discussion between the two reviewers until they reach consensus or through referral to an independent third reviewer. Final decisions will be recorded in a 'Risk of bias' table with a rationale for each decision.

Data

Synthesis

Results will be reported consistent with the PRISMA 2009 checklist; a PRISMA diagram and checklist will be included at the completion of the review.

In consideration of differing economic evaluation methodologies across sectors, a narrative synthesis of data will be undertaken. Narrative format 'Summary of Findings' (SoF) tables will present the key results of the review, including ranking of the certainty of the evidence upon which these results are based. Tables will be developed according to the outcome variable, or the means of reporting returns on investment. Information on population, intervention, comparison, setting and certainty of evidence will also be reported.

Primary comparisons will be made within sector (e.g. health sector using QALYs). Secondarily, cross sectoral comparisons will be explored using willingness-to-pay thresholds to convert health outcomes to monetary units.

Patient and public involvement

This research will be done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Discussion

This systematic review will be the first to consider cross-sector economic evaluation of investment in early childhood. Whilst this presents some methodological challenges, the results will provide invaluable information to assist in ranking whole-of-government priorities and forming policy recommendations. The project reflects a global perspective, with national policy implications.

The lack of consistent outcome measures between sectors represents a potential limitation of the review in comparing cost-effectiveness. For example, the conversion of outcomes to monetary units is contentious because of the assumptions required. Furthermore, benefits of early childhood intervention may be difficult to quantify because they are intangible (e.g. resilience or self-belief) or because of extrapolation methods of predicting far into the future (e.g. adult employment). Moreover, while the cost effectiveness and ROI of outcomes in the health, social welfare and education sectors can be measured or estimated, impacts on inequality, intergenerational outcomes and benefits at a societal level may be less easily quantified. Such limitations will be addressed transparently and within subgroups where necessary.

Summary evidence will identify gaps in the literature and provide policy makers with cross-sectoral information relevant to strategic decision-making for early childhood investment.

Ethics and dissemination plan

The findings of this review will inform policy makers and practitioners in public health, education, social welfare and primary care settings. A series of academic publications is planned, focussing on overall findings and subsets of data. Policy papers addressing key areas will be disseminated through Telethon Kids Institute networks to policy makers and practitioners. Exemption from ethics approval was granted by the University of Western Australia Human Ethics Office (RA/4/20/5677).

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Authors' contributions

Elizabeth Geelhoed (EG) led the conception and design of the study protocol and drafting the paper, and is the guarantor of the review.

Joelie Mandzufas (JM) contributed to the design of the study protocol and critical revision of drafts.

Phoebe George (PG) contributed to the design of the study protocol and critical revision of drafts.

Kenneth Strahan (KS) contributed to the design of the study protocol and critical revision of drafts.

Alison Duffield (AD) contributed to the design of the study protocol and critical revision of drafts.

Ian Li (IL) contributed to the conception and design of the study protocol and critical revision of drafts.

Donna Cross (DC) contributed to the conception and design of the study protocol and critical revision of drafts.

Acknowledgements

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The funders had no input to the design of the study or development of the protocol.

Competing interests

None declared.

Medline(Ovid)

1. exp Child, Preschool/
2. INFANT/
3. early childhood.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4. (preschool child* or infant* or prekindergarten or kinder* or child*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
5. 1 or 2 or 3 or 4
6. exp Cost-Benefit Analysis/
7. exp Quality-Adjusted Life Years/
8. (return on invest* or "cost and cost analysis" or economic evaluation or QALY or DALY or "quality adjusted life year*" or ROI or cost benefit*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
9. 6 or 7 or 8
10. 5 and 9
11. ("cost" or "costs").tw.
12. 10 and 11
13. limit 12 to yr="2000 -Current"
14. limit 13 to journal article
15. limit 14 to humans
16. limit 15 to ("all infant (birth to 23 months)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)")

Embase(Ovid)

1. exp Child, Preschool/
2. INFANT/
3. early childhood.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4. (preschool child* or infant* or prekindergarten or kinder* or child*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
5. 1 or 2 or 3 or 4
6. exp Cost-Benefit Analysis/
7. exp Quality-Adjusted Life Years/
8. (return on invest* or "cost and cost analysis" or economic evaluation or QALY or DALY or "quality adjusted life year*" or ROI or cost benefit*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
9. 6 or 7 or 8
10. 5 and 9
11. ("cost" or "costs").tw.
12. 10 and 11

13. limit 12 to yr="2000 -Current"
14. limit 13 to journal
15. limit 14 to human
16. limit 15 to (infant or preschool child <1 to 6 years>)

Psycinfo(Ovid)

1. early childhood.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
2. (preschool child* or infant* or prekindergarten or kinder* or child*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
3. 1 or 2
4. (return on invest* or "cost and cost analysis" or economic evaluation or QALY or DALY or "quality adjusted life year*" or ROI or cost benefit*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
5. 3 and 4
6. cost.mp. or costs.tw. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
7. 5 and 6
8. limit 7 to yr="2000 -Current"
9. limit 8 to peer reviewed journal
10. limit 9 to human
11. limit 10 to (100 childhood or 120 neonatal or 140 infancy <2 to 23 mo> or 160 preschool age)

Eric(ProQuest)

1.	Ab (early childhood or infant* or toddler* or child*) AND ab(cost*)
2.	Filter(2000-current date)
3.	Filter (Peer reviewed)
4.	Filter(scholarly journal articles)
5.	Filter(Early Childhood Education or Kindergarten or Preschool education)

EconLit(EBSCO)

S8	(AB child* OR AB (infant or infants) OR AB (baby or babies) OR AB (preschool or kindergarten or "early childhood education") OR AB newborn) AND (S4 AND S7) **Expanders** - Apply related words **Search modes** - Boolean/Phrase
S7	AB child* OR AB (infant or infants) OR AB (baby or babies) OR AB (preschool or kindergarten or "early childhood education") OR AB newborn **Limiters** - Scholarly (Peer Reviewed) Journals; Published Date: 20000101-20191231 **Expanders** - Apply related words **Search modes** - Boolean/Phrase
S6	AB child* OR AB (infant or infants) OR AB (baby or babies) OR AB (preschool or kindergarten or "early childhood education") OR AB newborn **Limiters** - Scholarly (Peer Reviewed) Journals **Expanders** - Apply related words **Search modes** - Boolean/Phrase

S5	AB child* OR AB (infant or infants) OR AB (baby or babies) OR AB (preschool or kindergarten or "early childhood education") OR AB newborn **Expanders** - Apply related words **Search modes** - Boolean/Phrase
S4	AB ("cost benefit analysis" or "cost-benefit analysis" or "cost effective analysis") OR AB ("economic outcomes" or "economic evaluation" or "cost effectiveness") OR AB cost analysis OR AB economic analysis OR "cost utility" **Limiters** - Scholarly (Peer Reviewed) Journals; Published Date: 20000101-20191231 **Expanders** - Apply related words **Search modes** - Boolean/Phrase
S3	AB ("cost benefit analysis" or "cost-benefit analysis" or "cost effective analysis") OR AB ("economic outcomes" or "economic evaluation" or "cost effectiveness") OR AB cost analysis OR AB economic analysis OR "cost utility" **Limiters** - Published Date: 20000101-20191231 **Expanders** - Apply related words **Search modes** - Boolean/Phrase
S2	AB ("cost benefit analysis" or "cost-benefit analysis" or "cost effective analysis") OR AB ("economic outcomes" or "economic evaluation" or "cost effectiveness") OR AB cost analysis OR AB economic analysis OR "cost utility" **Expanders** - Apply related words **Search modes** - Boolean/Phrase
S1	AB ("cost benefit analysis" or "cost-benefit analysis" or "cost effective analysis") OR AB ("economic outcomes" or "economic evaluation" or "cost effectiveness") OR AB cost analysis OR AB economic analysis OR "cost utility" **Expanders** - Apply related words **Search modes** - Boolean/Phrase

PEDE(SickKids)

The PEDE database will only show less than 300 articles at a time, if more it will cause you to refine your search. Therefore for this database by limiting the years searched

TITLE_ABSTRACT child* and TITLE_ABSTRACT cost* Limiters: neonates (0-1month, infants (1 month to 1 year) child 1-12 2000-2017 **1401 records, more than 300 please refine your search**
TITLE_ABSTRACT child* and TITLE_ABSTRACT cost* Limiters: neonates (0-1month, infants (1 month to 1 year) child 1-12 Limited: 2000-03
TITLE_ABSTRACT child* and TITLE_ABSTRACT cost* Limiters: neonates (0-1month, infants (1 month to 1 year) child 1-12 Limited:2004-05
TITLE_ABSTRACT child* and TITLE_ABSTRACT cost* Limiters: neonates (0-1month, infants (1 month to 1 year) child 1-12 Limited 2006-07
TITLE_ABSTRACT child* and TITLE_ABSTRACT cost* Limiters: neonates (0-1month, infants (1 month to 1 year) child 1-12 Limited 2007-10
TITLE_ABSTRACT child* and TITLE_ABSTRACT cost* Limiters: neonates (0-1month, infants (1 month to 1 year) child 1-12 Limited 2010-13
TITLE_ABSTRACT child* and TITLE_ABSTRACT cost*

Limiters: neonates (0-1month, infants (1 month to 1 year) child 1-12 Limited 2014-16
TITLE_ABSTRACT child* and TITLE_ABSTRACT cost* Limiters: neonates (0-1month, infants (1 month to 1 year) child 1-12 Limited 2017

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	4
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	60
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	10-30
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	287-298
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	299-302
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	300-302
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	303
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	72-103
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	104-105
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	108-129
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	131-138
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	139-152
STUDY RECORDS					

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	153-156
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	157-168
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	169-174
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	175-200
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	175-200
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	201-211
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	222-224
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐	☒	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐	☒	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	217-224
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	217-219
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	217-219