

Part 1: Background

A. Glossary of terms:

- **Body mass index (BMI):** BMI is defined as weight (kg)/height (meters)².
- **Case-series:** Report of a number of cases of a disease/condition.
- **Case-control study:** Retrospective comparison of exposures of persons with disease (cases) with those of persons without the disease (controls).
- **Cohort studies:** Follow-up of exposed and non-exposed defined groups, with a comparison of disease rates during the time covered.
- **Confidence interval (CI):** The range of numerical values in which we can be confident (to a computed probability, such as 90 or 95%) that the population value being estimated will be found. Confidence intervals suggest the strength of evidence. Where confidence intervals are wide, they indicate less precise estimates of effect. The larger the trial's sample size, the larger the number of outcome events and the greater the confidence that the true relative risk reduction is close to the value stated. Thus when the confidence intervals are narrow the "precision" is increased. In a "positive findings" study the lower boundary of the confidence interval, or lower confidence limit, should still remain important or clinically significant if the results are to be accepted. In a "negative findings" study, the upper boundary of the confidence interval should not be clinically significant if the result is to be accepted with confidence.
- **Confounding variable/Confounder:** A variable that can cause or prevent the outcome of interest, is not an intermediate variable, and is associated with the factor under investigation. A confounding variable may be due to chance or to bias. Unless it is possible to adjust for confounding variables, their effects cannot be distinguished from those of factor(s) being studied.
- **Dose-response relationship:** A relationship in which change in amount, intensity, or duration of exposure is associated with a change - either an increase or decrease - in the risk of a specified outcome.
- **Etiologic fraction (EF):** EF is a measure of the proportion of cases caused by an exposure in the exposed population. It is measured and expressed as a percentage.
- **Intrauterine growth restriction (IUGR)*:** A fetus or infant who has not attained his/her intrauterine growth potential. Most publications regarding this subject define IUGR as a birth weight below the 3rd centile or below the 10th centile for gestational age. Studies using a definition based on an infant's growth potential were included in this review.
- **Low birth weight (LBW):** Birthweight less than 2,500g.
- **Odds ratio (OR):** An odds ratio is calculated by dividing the odds in the treated or exposed group by the odds in the control group. When the OR is adjusted for confounding variables it is called an adjusted OR.
- **Preterm birth*:** Birth occurring prior to 37 completed weeks of gestation (includes 36 weeks and 6 days).

- **Prospective study:** Study design where one or more groups (cohorts) of individuals who have not yet had the outcome event in question are monitored for the number of such events, which occur over time.
- **Randomized controlled trial:** Study design where treatments, interventions, or enrollment into different study groups are assigned by random allocation rather than by conscious decisions of clinicians or patients. If the sample size is large enough, this study design avoids problems of bias and confounding variables by assuring that both known and unknown determinants of outcome are evenly distributed between treatment and control groups.
- **Relative risk or risk ratio (RR):** The ratio of the probability of developing, in a specified period of time, an outcome among those receiving the treatment of interest or exposed to a risk factor, compared with the probability of developing the outcome if the risk factor or intervention is not present.
- **Retrospective study:** Study designs in which cases were individuals who had an outcome event in question. Data are collected and analyzed after the outcomes have occurred.
- **Small for gestational age (SGA):** An infant below the 10th centile for weight for his/her gestational age (some studies have used the definition of an infant below the 3rd centile).
- **Systematic review/Meta-analysis:** A review in which bias has been reduced by the systematic identification, appraisal, synthesis, and, if relevant, statistical aggregation of all relevant studies on a specific topic according to a predetermined and explicit method.
- **Very low birth weight (VLBW):** Birthweight less than 1,500g.
- **Weighted mean difference (WMD):** A method used to combine measures on continuous scales (such as weight), where the mean, standard deviation and sample size in each group is known.

*The terms “prematurity” and “intrauterine growth retardation” have been used in the past but in the recent literature they are commonly replaced by the more appropriate terms **preterm birth** (born preterm) and **intrauterine growth restriction**. Wherever possible in assessing the impact of a factor or an intervention we attempted to distinguish SGA from IUGR, but when not possible these terms were used interchangeably.

B. Introduction:

Birth weight is the most important determinant of perinatal, neonatal and postneonatal outcomes.^{1;2} Poor growth during the intrauterine period increases the risks of perinatal and infant mortality and morbidity.^{1;3;4} In addition, the intrauterine milieu affects the health of an individual not only during fetal life but also throughout the postnatal stages of life.^{5;6} Compositional changes are noted in the developing brain exposed to an adverse intrauterine environment and/or fetal malnutrition.⁷ Adverse intrauterine environment results in either low birth weight (LBW) or preterm birth. LBW is a multifaceted problem that includes a wide spectrum of health related problems from its origin to the consequences later in life.^{5;6} Similarly preterm birth is also of significant public health importance because of its association with an increase in mortality and childhood morbidities such as developmental problems, cerebral palsy, learning difficulties, and an increased risk of sudden infant deaths.^{2;4}

The birth weight of an infant is dependent on the length of the gestation and the intrauterine growth of the fetus. LBW can result from preterm birth or intrauterine growth restriction (IUGR) or a combination of the two. A preterm infant can be large for gestational age (rare), appropriate for gestational age or small for gestational age. LBW does not necessarily mean IUGR and vice versa. There may be significant overlaps among these groups of infants, which stresses the importance of a correct estimation of the gestational age of the newborn. Infants born at relatively mature gestation (32-36 weeks) are still at higher risk of death during infancy compared to term infants.⁸ As there are more infants born in this gestational age stratum compared to lower gestational ages they have a marked impact on health care utilization and costs. For each preterm LBW infant born in Canada, the neonatal intensive care and postneonatal cost up to one year of age was conservatively estimated at \$ 8,443 in 1987 and \$ 48,183 in 1995 per surviving LBW infant.⁹ The lifetime cost for permanent handicaps of neonatal origin were estimated to be \$ 676,800 per preterm LBW infant. A population based prevention strategy, which reduces the preterm birth rate by 20%, could save 2-billion dollars/year in health care costs nationally.⁹

Growth restricted infants represent a heterogeneous group of infants who have not reached their in-utero growth potential.^{1;10} Intrauterine growth restriction (IUGR) is associated with increased risk of neonatal death in very low birth weight infants (VLBW) [odds ratio (OR) 2.77, 95% confidence interval (CI) 2.31, 3.33].¹¹ The extent of the impact depends on the underlying mechanism and timing of the insult.¹⁰ Viral infections in the first trimester of pregnancy lead to symmetrical growth restriction (head circumference and weight) but utero-placental insufficiency in the later part of pregnancy leads to asymmetric growth restriction (discrepancy between head circumference and weight). LBW is closely related to preterm birth as it is estimated that approximately 50% of preterm infants weigh less than 2,500 grams while only 2% of full-term infants weigh below 2,500 grams.¹² Epidemiologists in the field are faced with the challenges of assessing the differential consequences of these components and at the same time separating the preterm component of LBW.¹³

This review analyzes the evidence for the determinants or causative factors, and the strategies for prevention of adverse pregnancy outcomes related to preterm, LBW, IUGR or small for gestational age (SGA) births.

C. Burden of illness:

a. Global:

IUGR and LBW infants represent a significant health problem worldwide.^{1;14-17} The IUGR-LBW rate is highest in South-Central Asia followed by Middle and Western Africa, Oceania and Latin America.¹⁸ The significance of these findings should be understood within the context that 75% of these infants are born in Asia (greater total number of live births) while a small number of children are born in Oceania. These rates of IUGR-LBW are probably underestimates of the global situation as in the developing world a significant proportion of infants are born at home and are not registered as live births.¹⁸

The incidence of preterm birth is increasing. This rise is particularly noted in developed countries (the quality of data from the developing countries precludes any firm conclusions).^{14;16;19-21} Dramatic reductions in mortality rates have been reported in the last 2 decades among preterm infants with less of a reduction in morbidity.^{14;22} In the developed countries only France and Finland reported a reduction in preterm birth rates²³ until the early 1990's. However, the rates for LBW births have been reported to be on the rise again in Finland (4.4% rate for LBW births in 1998 compared to 4.0% in 1991).²⁴ The increase was chiefly attributed to a rising incidence of multiple births.²⁴ LBW/preterm birth rates are higher in the US compared to other developed countries and are believed to contribute to higher infant mortality in the US compared to other industrialized nations despite technological advances.²²

b. National (Canada):

The rate of LBW among live born infants in Canada was 5.77% in 1995. This was a significant decline from 6.64% in 1975. However, there was a slight increase in the LBW rate, 5.77% in 1995 compared to 5.53% in 1985.¹² This rate was still higher than that reported from some European countries (Finland 4.0% in 1985, Ireland 4.4% in 1987, Norway 4.5% in 1985).¹⁸

The incidence of preterm birth has increased in Canada (excluding Ontario) (6.4% in 1981 to 6.7% in 1992 and 7.1% in 1997).^{20;21} This increase is secondary to an increase in multiple births, an increase in obstetrical interventions, an increase in the registration of early gestation births and an increase in the use of ultrasound to estimate gestational age.²⁰ Higher incidences of preterm birth in twins and higher order pregnancy have been noted.²¹ However, the major contribution (80%) to the increase in the preterm birth rate relates to singleton pregnancies.²¹

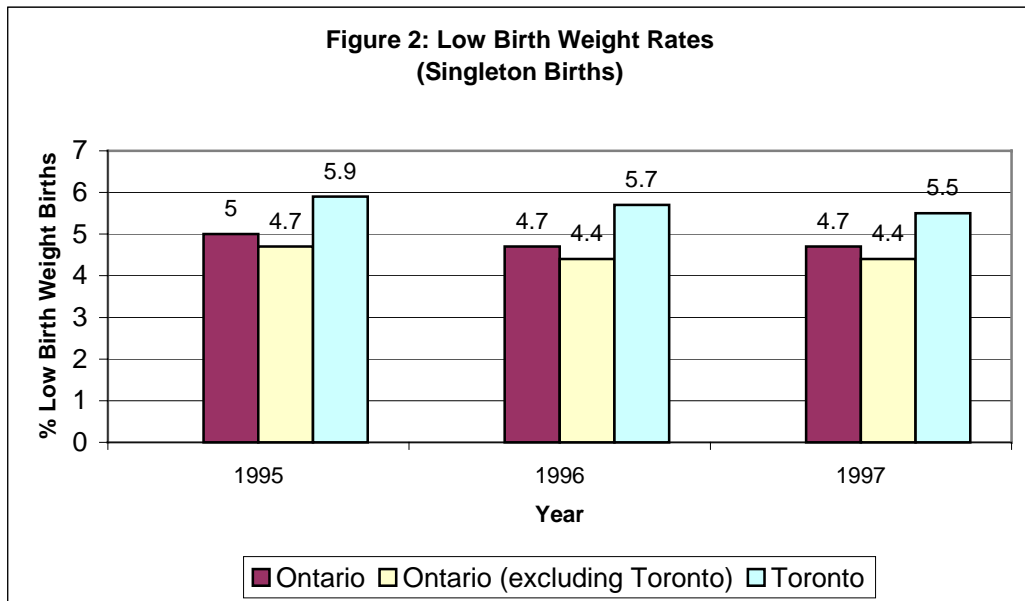
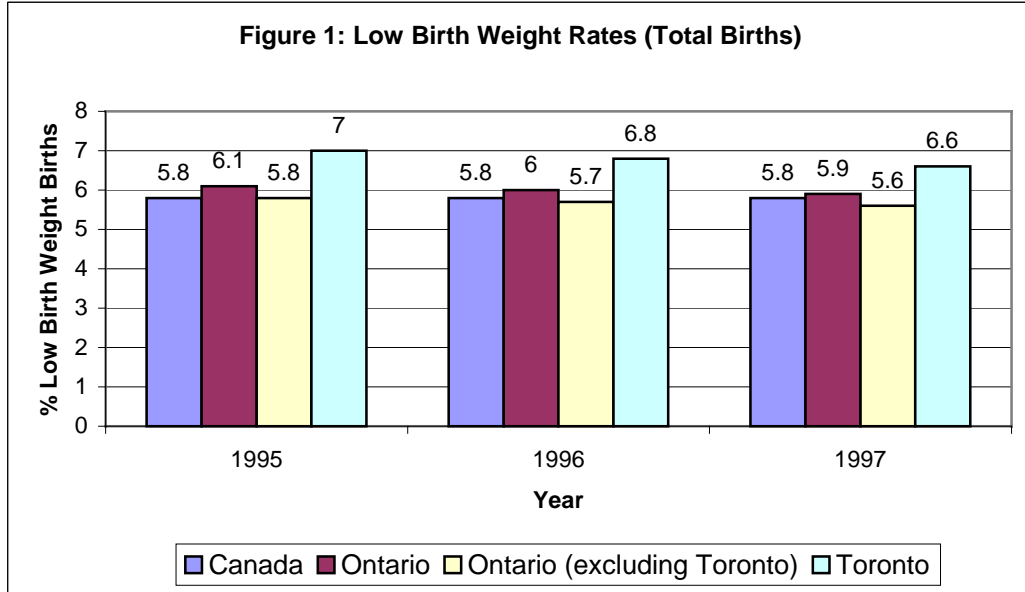
c. Provincial (Ontario):

The rate of LBW among singleton live births in Ontario decreased from 1995 to 1997 (5.0% in 1995, 4.7% in 1996 and 4.7% in 1997) (Toronto Public

Health) (fig. 1,2). Preterm birth rates for Ontario are not included in this report due to data accuracy concerns.

d. Local (Toronto):

LBW rates for singleton live births have been consistently higher for Toronto compared to Ontario over the period 1986-1997. The rates of LBW among singleton live births were 6.0% in 1993, 5.9% in 1994, 5.9% in 1995, 5.7% in 1996 and 5.5% in 1997. These rates are well above the rates for the province of Ontario (5.0, 4.9, 5.0, 4.7 and 4.7% respectively). (Toronto Public Health) (fig. 1,2). The preterm birth rates for Toronto are not included in this report due to data accuracy concerns.



Source: Canadian rates: Statistics Canada, Vital Statistics, Birth Database.

Source: Ontario and Toronto rates: Live Birth Database, Health Planning System (HELPS), Ministry of Health & Long Term Care (MOHLTC)

Data Limitations: A number of live births are not reported in the Ontario vital statistics each year. This number increased in 1996 and again in 1997. It is estimated that 2.3% of Ontario live births and 3.2% of Toronto live births were not reported in 1997. The number under-reported is disproportionately higher among mothers under 20 years of age, low birth weight births and pre-term births. Therefore, the number of low birth weight births in 1997 may be higher than reported. Provided by: Health Information, Toronto Public Health.

D. Data accuracy:

The three components of an effective surveillance system are data collection, data analysis and response. Concerns about data accuracy have prevented the Canadian Perinatal Surveillance System of Health Canada from

including the data from the Province of Ontario in its many peer-reviewed publications.²⁰ The data regarding preterm birth rates for Ontario and Toronto are not included in this report due to concerns about accuracy in the reporting of gestational age in the Ontario vital statistics database.

According to UNICEF every child has the right to civil registration at birth – thus being entitled to the civil rights (including recognition as a person) in the jurisdiction of birth.²⁵

Results of a study by the Central East Health Information Partnership²⁶ show that the percentage of unregistered births (birth events not included in the official Ontario vital statistics data) in Ontario increased from less than 1% in the early 1990s to over 3% in 1998. The percentage of unregistered births is higher among mothers below 20 years of age, low birth weight births and preterm births. The rates of preterm/small for gestational age/low birth weight/intrauterine growth restricted births are likely to be underestimated in the Province of Ontario and Toronto. The introduction of birth registration fees by some municipalities (including Toronto) in 1996/1997 appears to have negatively affected the registration process. Municipalities with birth registration fees were found to have a greater prevalence of unregistered births. In the event of an early neonatal death there is no incentive for parents to register the birth of their child. This could account for a serious element of bias in the reporting of Ontario vital statistics.

E. Objectives of the review:

Evidence based practice is the “conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients”.²⁷ Based on this principle the objectives of this systematic review were to critically appraise the available evidence from systematic reviews, meta-analyses, and narrative reviews, regarding

- (a) The contributors/factors/determinants related to preterm/SGA/LBW/IUGR births and
- (b) The effectiveness or efficacy of strategies/approaches/interventions to prevent preterm/SGA/LBW/IUGR births.

The interventions that were examined in this review included currently recommended interventions undertaken in clinical practice as well as newly proposed interventions.

This review will help to guide Toronto Public Health initiatives to address the issue of preterm/LBW/SGA/IUGR births.

F. Method of review:

a. Search strategy:

A comprehensive literature search was carried out. The search strategy commenced with a search of personal files and review articles currently available within “Toronto Public Health”.

Electronic databases were searched using the draft search strategy developed within “Toronto Public Health” with the addition of relevant terminology identified in various databases. Only published studies were identified. The following databases were searched.

- MEDLINE (1966-2001)
- Embase (1992-2001)
- CINAHL (1992-2001)
- Cochrane Library- Issue 1, 2002
- PsycInfo (1992-2001)
- ERIC (1992-2001)
- Sociological Abstracts (1992-2001)
- Dissertation Abstracts (1992-2001)
- Social Sciences Citation Index (SSCI) (1992-2001)
- WHO reproductive health library (2000) No. 3
- Social Work Database (1992-2001)
- Relevant project monographs (1994-2001)

Book chapters were identified through various databases. The reference lists from recent textbooks, reviews, and reports of primary studies were examined to include additional material. The retrieval was limited to English language of publication only (due to time constraints). The number of articles scanned, selected and retrieved from each database is listed in appendix 1.

The search was updated throughout the data collection stage of the project (until February 10, 2002). This consisted of periodic re-running of the MEDLINE and current contents search strategies. Recently published issues of the key content specific journals (Pediatrics, J Pediatr, New Engl J Med, Lancet, and Am J Epidemiol) were searched manually. A librarian was consulted to design and verify the comprehensiveness of the search strategies.

Determinants: The following terminology was used (major subject headings were further explored using explode function in the databases):

- **Study designs** assessed were: Meta analyses, systematic reviews, literature reviews, Cochrane reviews, and narrative reviews, clinical trials, randomized controlled trials, controlled clinical trials
- **Key words** used were: infant, newborn, preterm birth, prematurity, immaturity, immature labor, premature labor, small for date, low birth weight, growth or growth diseases, IUGR, SGA, fetal growth retardation, infant sex, sex ratio, race, racial stocks, minority groups, culture, ethnic groups, ethnicity, acculturation, biculturalism, cultural conflict, ethnic neighborhoods, cultural pluralism, biraciality, maternal age, adolescent pregnancy, paternal age, multiple pregnancy, unwanted pregnancy, body constitution, maternal height, marital status, paternal height, paternal weight, maternal birth weight, maternal nutrition, parity, past history, prior history of low birth weight, general morbidity, episodic illness, prior history of spontaneous abortion, prior still birth, neonatal death, prior history of prematurity, prenatal exposure, neonatal diseases, family, life style, smoking, passive smoking, tobacco, tobacco related disorders, alcohol, drinking behavior, stress, anxiety, drug abuse, substance abuse, caffeine, marijuana, cannabis, hashish, crack cocaine,

narcotics, illicit drugs, heroin, cocaine, methadone, substance related disorders, over the counter medicine, herbal remedies, complementary medicinal use, medicinal plants, non-prescription drugs, plant extracts, street drugs, designer drugs, infection, inflammatory responses, intrauterine infection, urinary tract infection, psychological factors, poverty, socioeconomic status, caloric expenditure, exertion, activity, strenuous work, physical work, work scheduling, exercise, abuse, violence, social support, antenatal care, prenatal care, preconception care, malformations, genetic disorders, workplace hazards, environmental pollution, tobacco smoke pollution, health education, environmental hazards, toxins, noise, body constitution, body height, weight, weight gain, body weight, caloric intake, vitamin, multivitamin, education, anemia, nutrient deficiency, prepregnancy weight.

Interventions: The following terminology was used.

- **Population:** community wide, population, population base, adolescents, teens, teenagers, elderly, low income, low socioeconomic status, poverty, high risk, at risk, low income neighborhood, at risk neighborhood
- **Interventions:** efficacy, effectiveness, impact, evaluation for each intervention
- **Study designs:** narrative review, meta-analysis, systematic review, Cochrane review, randomized controlled trial, controlled clinical trial, and interventional study, control group
- **Outcomes:** low birth weight, preterm birth, prematurity, underweight baby, IUGR, SGA

b. Inclusion criteria:

The purpose of this review was to summarize the recent evidence available from systematic reviews, narrative reviews and meta-analyses on each determinant and strategies of prevention (appendix 2). When not possible to identify a review an attempt was made to describe the data from available primary studies.

Explicit inclusion criteria with a view to answer the clinical research question were used for selecting reviews. A review was considered only if it satisfied the criteria of

- Study Design
- Population
- Intervention
- Determinants
- Comparisons
- Outcomes

The selection criteria were categorized to allow for the elimination of reviews that did not provide information relevant to this review or information that was obtained from already included reviews. A list of excluded reviews is provided in appendix 3.

c. The selection criteria:

After identifying the existence of reviews of interest, the following phases

marked the selection procedure.

1. Both authors (PS, AO) individually assessed the titles, abstracts, and key words for each citation.
2. A review was retrieved as full publication if its title, abstract or key words suggested that the review was likely to have information regarding the research question.
3. Any difference of opinion particularly regarding the content made it mandatory to retrieve the review for clarification.
4. Assessment of eligibility of the review article was performed using a form by one author (PS) and each article was assessed for methodological rigor by both (PS and AO) authors.
5. All differences in the opinions were resolved by consensus.

d. Data abstraction:

This followed a stepwise procedure.

1. One reviewer (PS) abstracted and documented the content of each included review.
2. This included:
 - a. Description of each review
 - b. Year of publication
 - c. Type of review - Cochrane review, meta-analysis, narrative review etc.
 - d. Details on design of review
 - e. Search strategies
 - f. Demographic characteristics of the population
 - g. Primary outcomes
 - h. Secondary outcomes
 - i. Side effects, if applicable

Data abstraction from systematic reviews, literature reviews, narrative reviews and included primary studies was performed.

e. Assessment of the methodological quality of reports:

The quality of each systematic review/meta-analysis related to determinants and interventions was assessed according to the guidance from the QUOROM statement (appendices 2 and 4).²⁸ This method includes detailed assessment of abstract, methodology of literature review, results, discussion and comprehensiveness of the review. The reviews for which data were abstracted regarding epidemiological association or effectiveness of interventions were also assessed for selection bias, quality assessment of the studies and data synthesis (appendix 2). When a review was not identified for a particular determinant or intervention, selected primary studies were described. The authors do not claim this to be comprehensive. The primary studies were also assessed on the basis of sample selection, confounder assessment, data collection methods, attrition rate and analysis. If for a determinant the review did not address the issue of criteria of causation a primary study describing that association was discussed after the description of the review. Occasionally the authors identified studies that examined the impact of a certain determinant on a

subgroup; the results from such studies are reported for interest.

As predicted the authors found multiple reviews on certain subjects published at different time points that had some data abstracted from the same randomized controlled trials. This was identified and reported in the text. These results are summarized in terms of ranges of the point estimates, when possible, with clear documentation in the text.

G. Format of the report:

The causative factors or the determinants for preterm/SGA/LBW/IUGR births are interrelated. It is difficult sometimes to separate out the impact of a determinant/intervention on the outcome of interest. Each factor was reviewed individually and an attempt was made to assess its significance to individual outcomes.

Each determinant is discussed with the basic principles for causation (biological plausibility, specificity, temporal relationship, consistency, strength, dose response and human experimentation). An attempt was made for each determinant first to delineate biological plausibility, followed by the strength of the epidemiological association and the available evidence for the effectiveness of interventions to improve the outcomes from the reviews on the subject. When an additional study not included in the review or published after the latest review or of interest was found a separate description was provided. If no review was identified for a determinant, a review of major individual studies in the area was performed. For the purpose of simplicity if the determinant is modifiable and, attempts to circumvent the determinant have been described in the literature, the evaluation of these strategies was performed at the same time.

The strength of the evidence for each determinant was assessed. Determinants with proven association (information from the epidemiological studies satisfying most of the causality criteria), possible association (information from the epidemiological studies satisfying some of the causality criteria but further research is needed), and no association (information from the epidemiological studies not indicative of causal association) were identified. Potential determinants for which no information was available were also identified.

The strength of the evidence was assessed for various interventions/strategies to prevent preterm/LBW/SGA/IUGR births. Interventions/strategies were identified as having strong evidence of effectiveness (cumulative evidence from well designed meta-analyses or systematic reviews indicative of effectiveness), probable evidence of effectiveness (some evidence from systematic reviews or randomized controlled studies or clinical studies indicative of effectiveness), evidence that they may be effective (evidence from clinical and/or epidemiological studies of the causality for the determinant, however intervention studies are non-existent or poorly designed) or evidence that they were not effective (cumulative evidence from well designed meta-analyses or systematic reviews indicative of ineffectiveness). Interventions/strategies were identified for which there was a lack of/inadequate information.