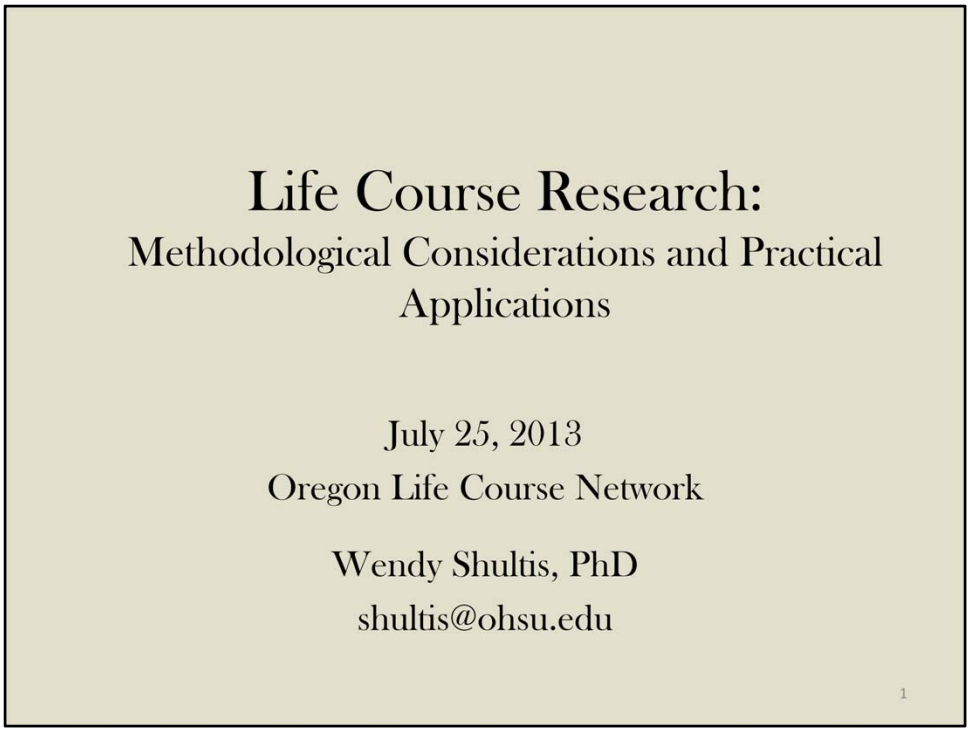
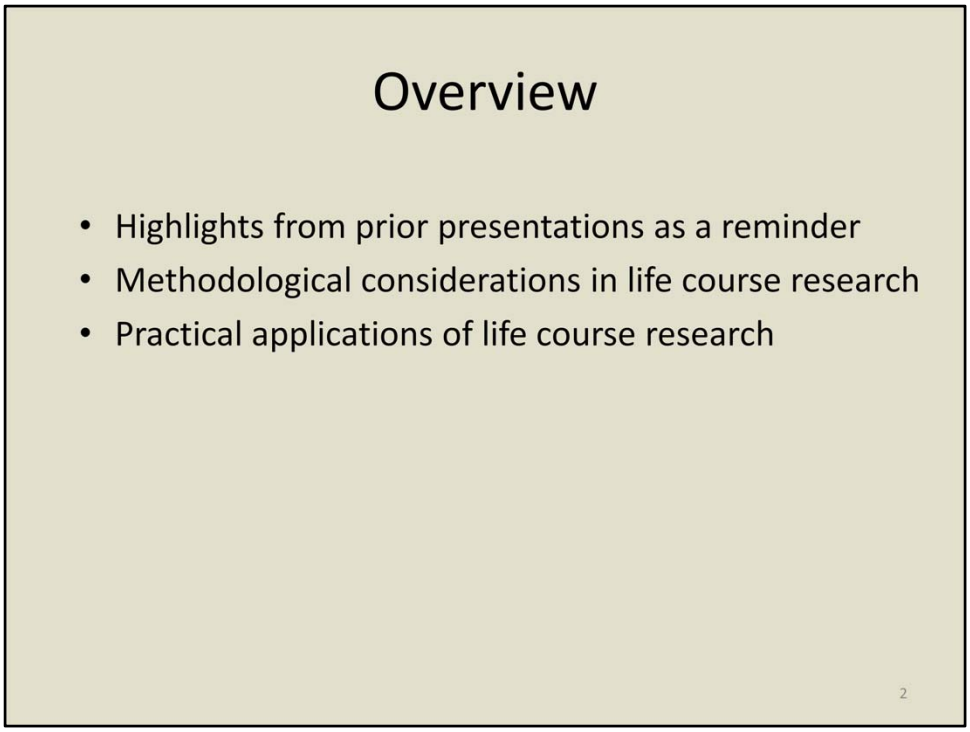
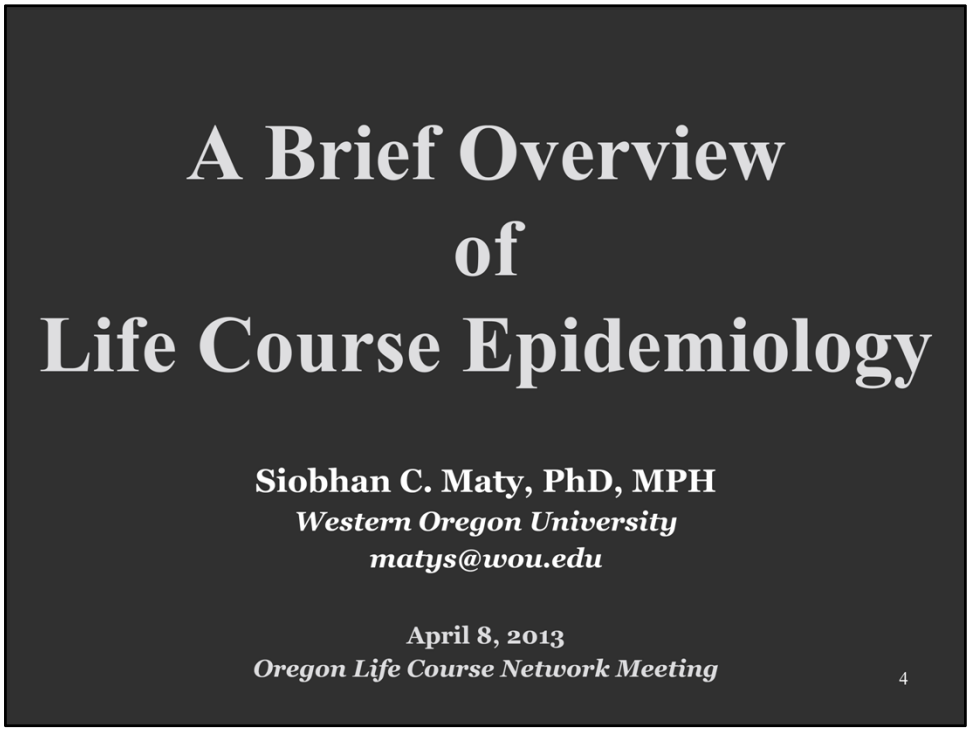


Slide 1:
Hello. I am Wendy Shultis and I'm going to be giving presentation number 3 in this series, the aim of which was to provide some background for folks on life course research. To give you a little background on myself, I have a PhD in epidemiology from the University of Bristol in the SW of England. I did my post-doc at the NIH, and then moved to the University of Washington briefly before going to WA State Department of Health. I have worked in or around life course research for several years. More recently though, I have embarked on a career change and am back at school training to be a nurse midwife. I am currently a student at OHSU's school of nursing.

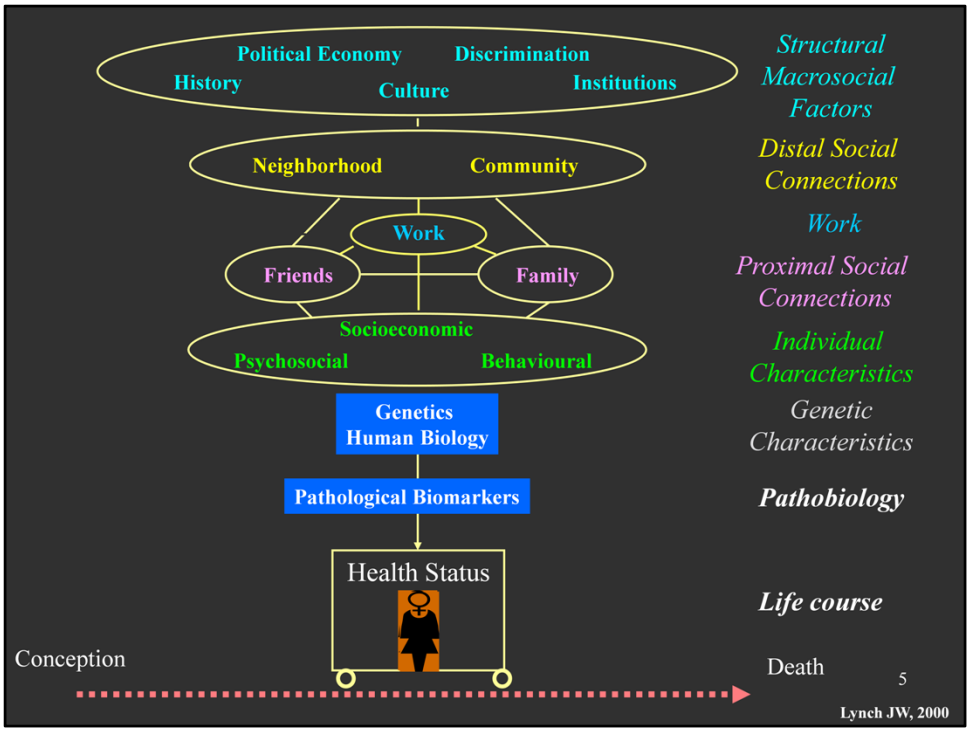


Slide 2:
In my presentation today, I am going to start by reviewing the highlights from the prior two talks to serve as a reminder of what we have heard to date, and to help those who might have missed one of the talks to catch-up. Then, I am going to talk briefly about some of the over-arching methods behind life course (how do we know what we know), I'll explain what a meta-analysis is and how to read one, before moving on to some of the statistical issues being discussed currently in the literature around adjusting for intermediates and gestational age. Finally, I will talk about some of the practical applications of life course research.

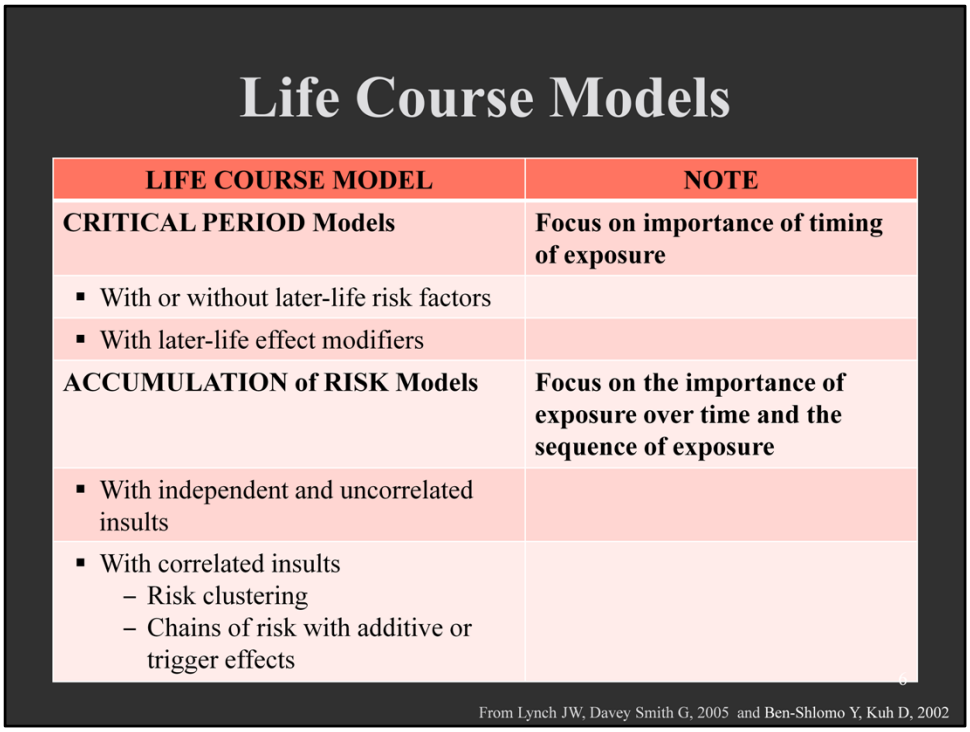
Slide 3:
Highlights from prior presentations in the series.



Slide 4:
On April 8th, Siobhan gave the first presentation to the group. She talked about what life course is in this context, which is the study of how chronic disease development is influenced by social and environmental determinants of health experienced at different stages over the life course.

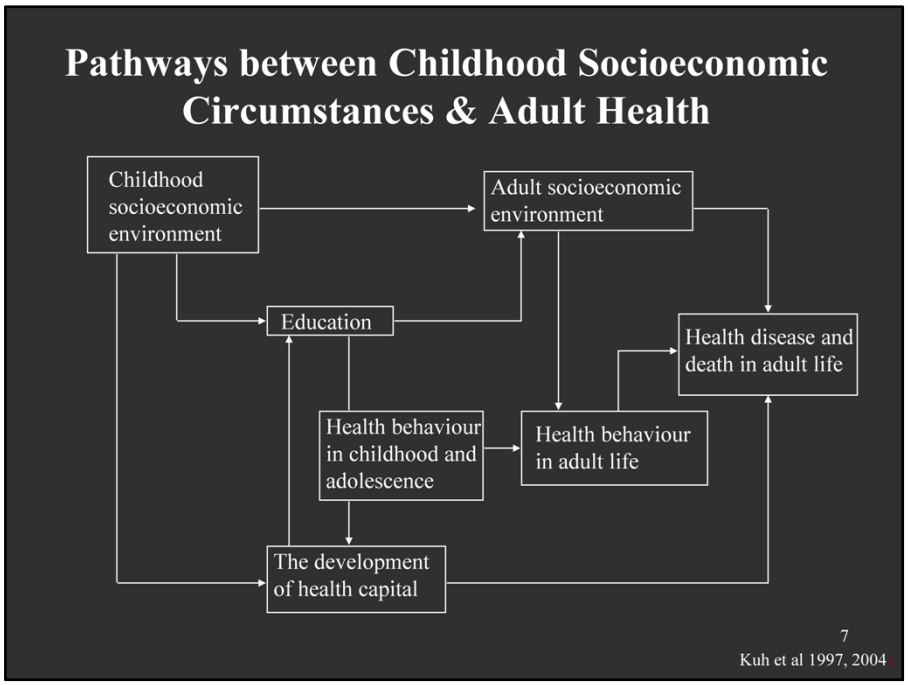


Slide #5:
Siobhan talked about the multiple layers of factors that influence health from the politics, history and culture of our society, to the neighborhood and community we live in, to our work and social connections, to our individual characteristics such as behaviors, to genetics and biomarkers, and how they combine and interact to influence health between conception and death.

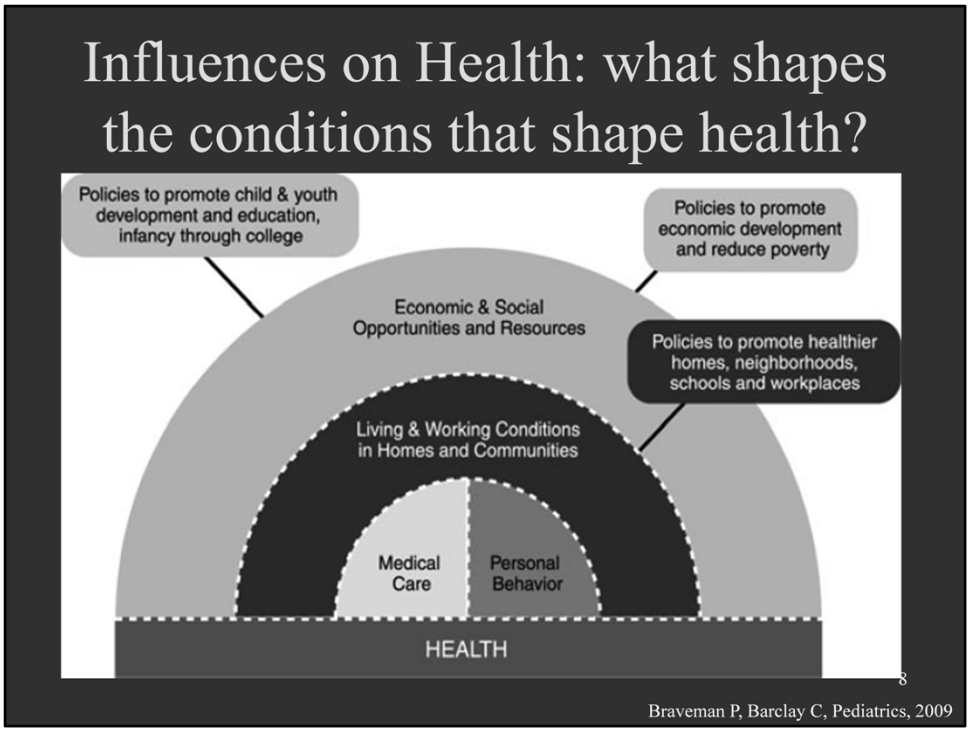


Slide #6:
Siobhan talked about the different over-arching life course models including critical periods, in which our bodies are particularly sensitive to an exposure. Examples Siobhan included were thalidomide use in pregnancy (to treat morning sickness in the late 1950s and early 1960s) which affected how the limbs of the baby were formed, and the impact of poverty during important childhood social transitions such as school entry. These are critical periods, such that once they have happened, you never get another chance at a re-do.

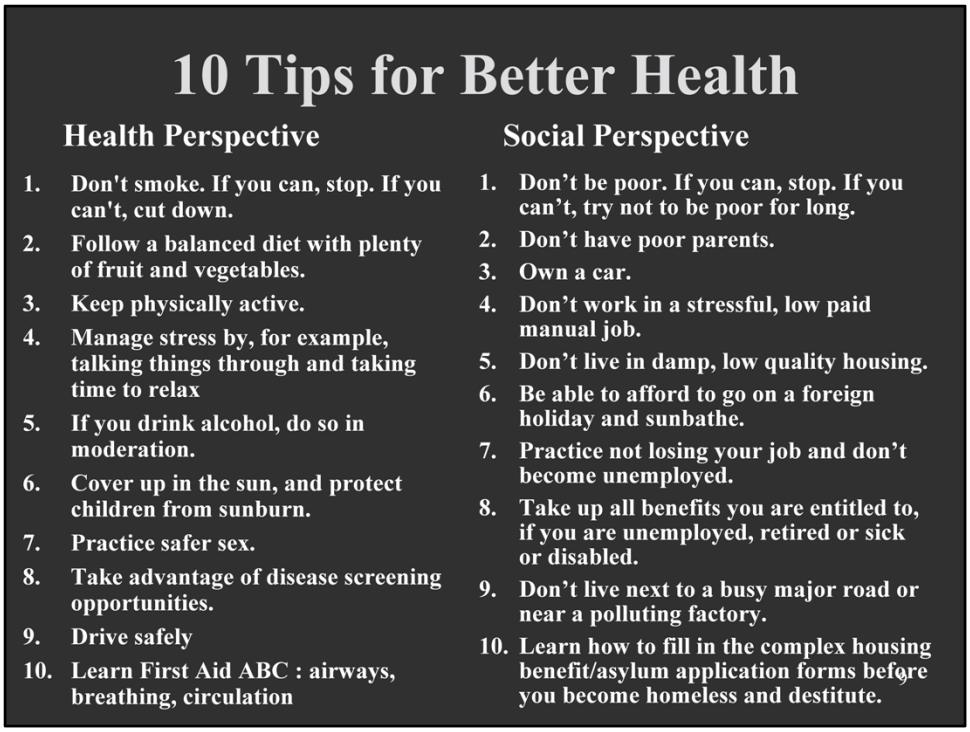
And, accumulation-of-risk models in which the different exposures gradually accumulate over time through episodes of illness, adverse environmental conditions and health damaging behaviors. Examples Siobhan gave included the clustering of exposures such that children from poorer socioeconomic backgrounds are more likely to be of low birth weight, have poorer diets, be exposed to passive smoking and have fewer opportunities for physical activity. And then chains of risk such that becoming overweight in childhood may cause reduced physical activity in adolescence.



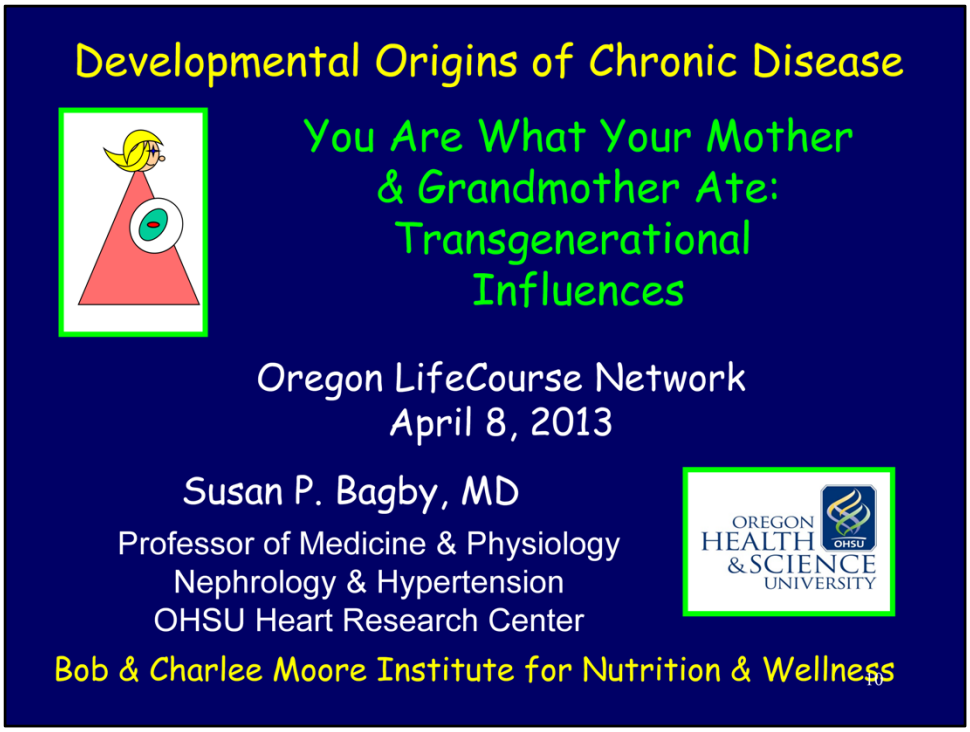
Slide #7:
Siobhan addressed the pathways and inter-connectivity between childhood socioeconomic circumstances and adult disease, and you will see the importance here of education and the development of health capital.



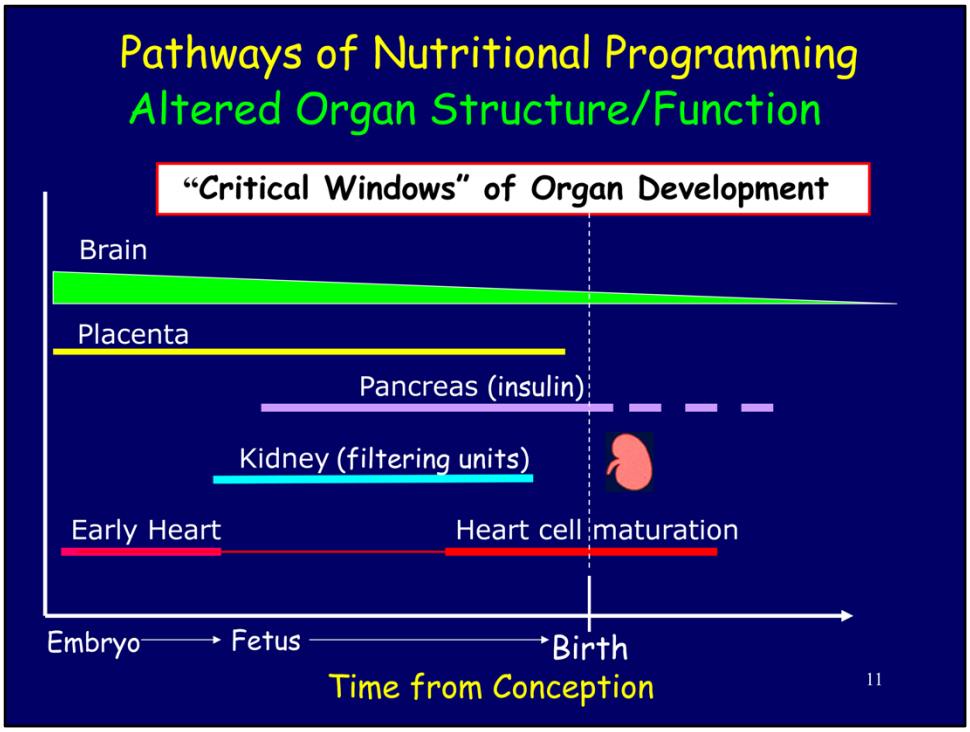
Slide #8:
Then, in this figure, which is another way of illustrating the multiple layers of factors that influence health, Siobhan highlighted how we can promote health at different levels through policy changes, both at the societal level promoting education, economic development and reduction in poverty, and then at the community level by promoting healthier homes, neighborhoods, schools and workplaces.



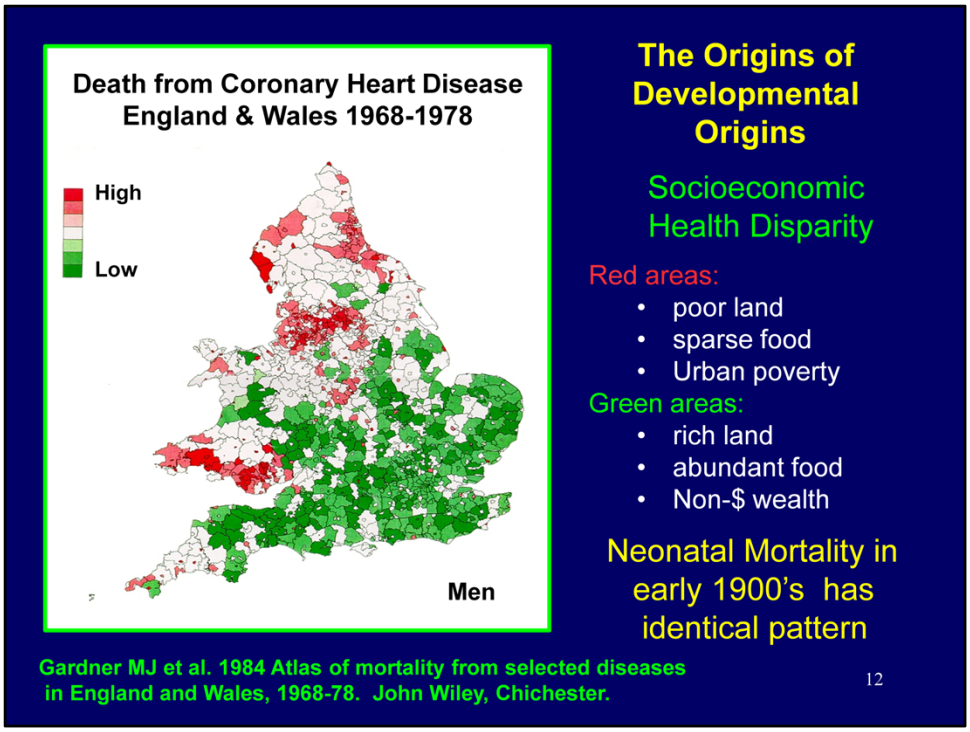
Slide #9:
Finally, Siobhan ended her presentation with some handy tips for better health, and I draw your attention to the social perspective. Don't be poor; if you can, stop; and if you can't, try not to be poor for long. Don't have poor parents. Don't live in damp poor housing. Practice not losing your job and don't become unemployed.



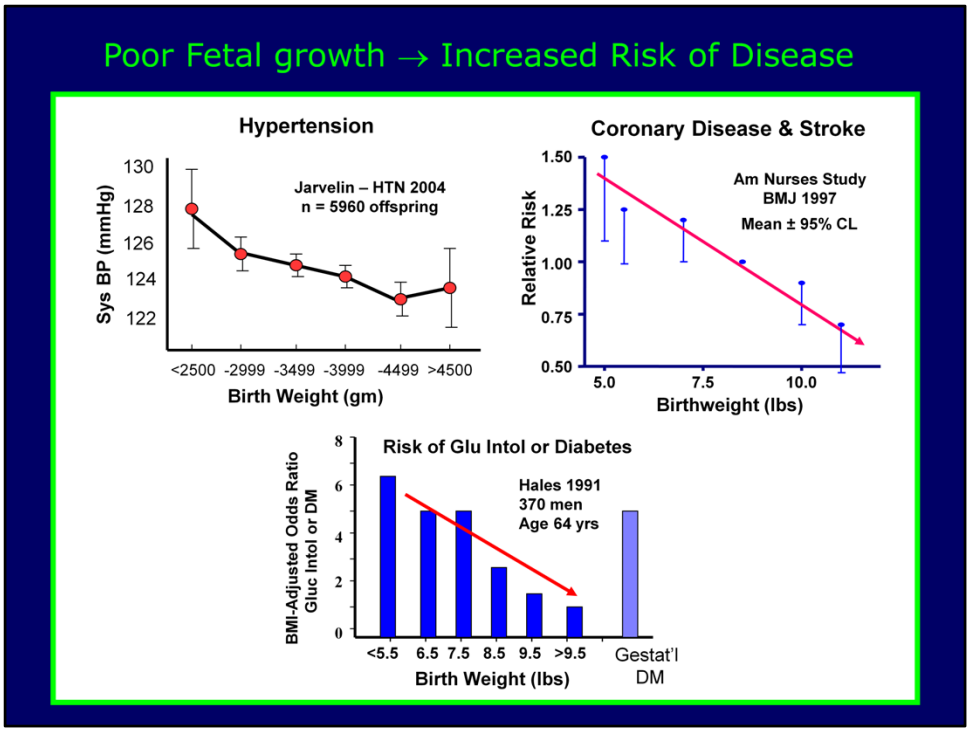
Slide #10:
Then on June 7, Susan talked further about the developmental origins of chronic disease.
[Note: this presentation was originally scheduled for April 8 but was postponed to June 7.)



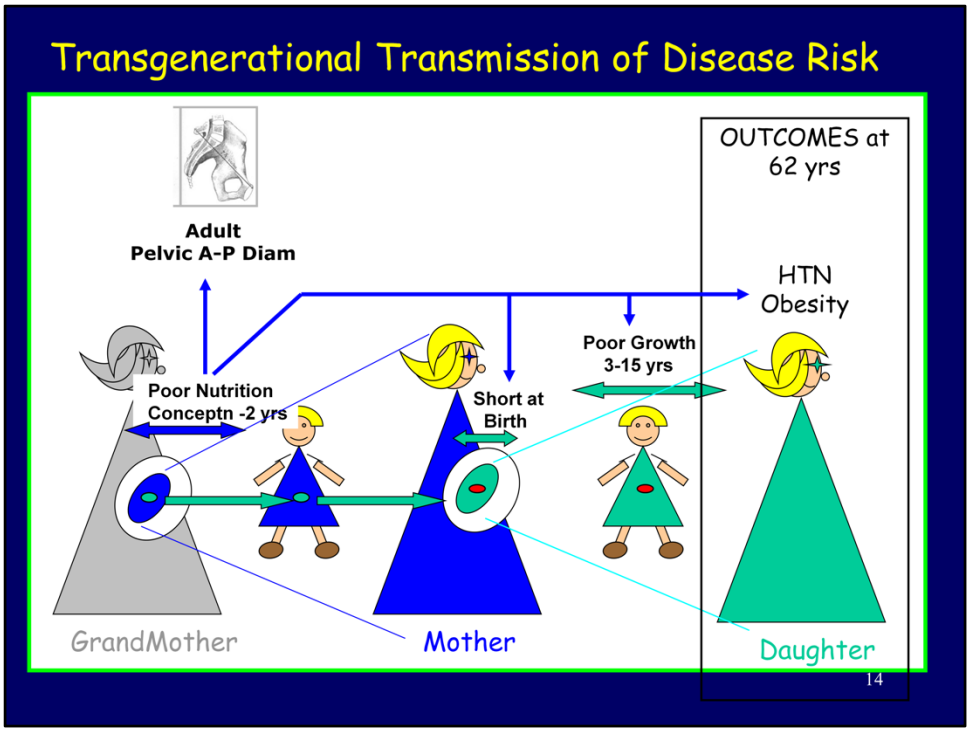
Slide #11:
Building on Siobhan's introduction to critical periods, Susan talked about exactly when during pregnancy each of the body's major organs develop and how this means that exposures at different times in pregnancy and early life are likely to have effects on different organs and body systems, which in turn affects likelihood of disease in that body system later on.



Slide #12:
She gave some historical perspective, talking about some of the original observations that started off the field of life course research. Namely, the studies in England and Wales which connected geographical distributions of neonatal mortality in the early 1900's with later death from coronary heart disease. People living in parts of the country with high rates of neonatal death (signifying sub-optimal pregnancy and early life circumstances) had higher death rates from heart disease in middle and older ages.

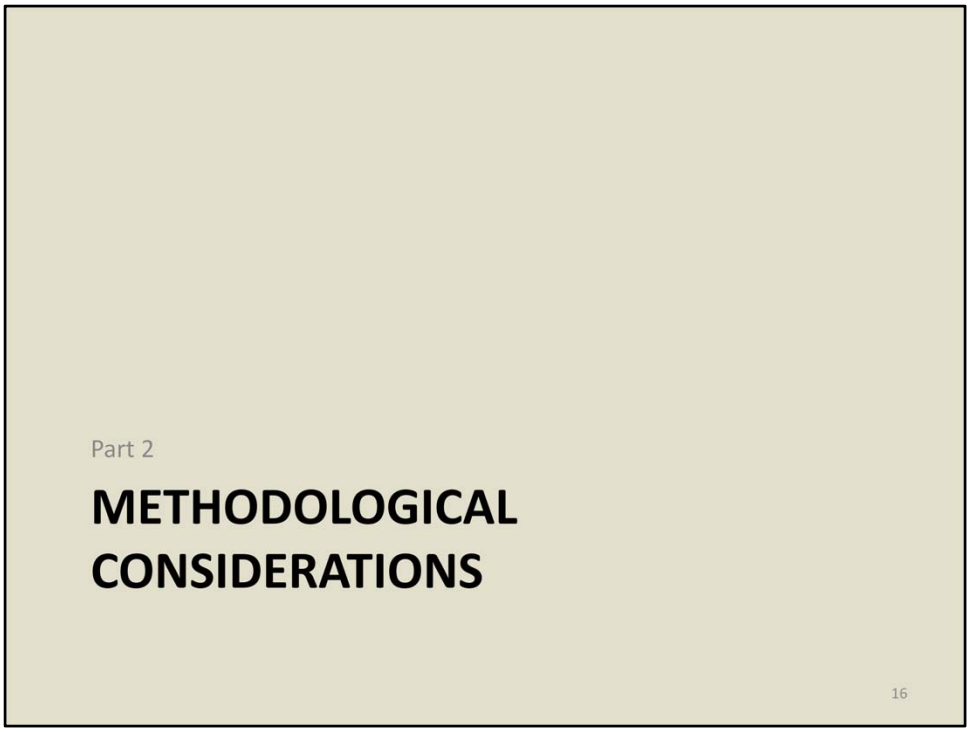


Slide #13:
Susan showed us these graphs of birth weight with different chronic diseases including hypertension, cardiovascular disease and diabetes, which illustrated the findings from several studies showing people born with lower birth weights (signifying sub-optimal pregnancy circumstances) were at higher risk for getting these chronic diseases in later life. You can see here that all 3 of these graphs show the same pattern, sloping down (so lower risk) at higher birth weights.

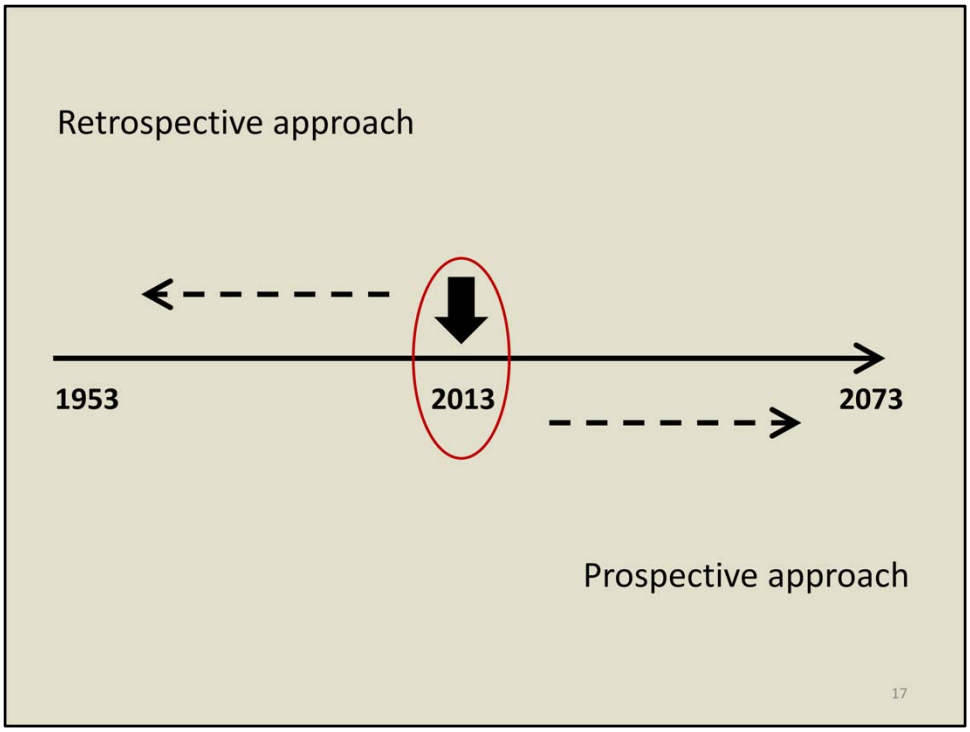


Slide #14:
Susan also talked about how these effects can be passed on from one generation to the next. The example she gave was on how poor nutrition in one generation can lead to women having babies that are short at birth in the next generation who exhibit poor growth during childhood which puts them at greater risk of hypertension and diabetes when they are in middle age.

Slide #15:
Finally, Susan ended her presentation by suggesting we should focus interventions on girls and mothers to be, and to harness the village to change the culture. So that gives you a reminder of what has been discussed to date in prior presentations.



Slide #16:
Now to methodological considerations. How do we know what we know, and what are the specific issues we need to consider when reviewing life course research and planning our next steps.



Slide #17:
Two over-arching approaches to life course research include (1) selecting a representative group of people today, measuring their health (or disease) status now and going back in time either by gathering birth records, records kept by school nurses or doctors, military records, and hospital records or by asking people to try and remember things like their birth weight, and trying to piece things together (to re-create) the happenings of their life so we can study how exposures over the life course affect disease in later life; a retrospective approach. Or, (2) selecting a representative group of people now, measuring things like their birth weight, parent's socioeconomic status, housing, diet in pregnancy and childhood, and then following them as they age and collecting data on further exposures and disease; a prospective approach.

The advantages of a retrospective approach is that it is quicker. The disadvantages are that you don't have any control over how the data 50 years ago were collected, the opportunity for quality control over how things like birth weight or diet were measured has long gone, and often people's records or memories from way back are patchy at best. Moreover, when we are asked to recollect or self-report things, we have selective memories and see the world as we would like it to be. For example, women who have lost children to leukemia may be more likely than women with healthy children to remember having X-ray procedures during pregnancy. And, men tend to over-estimate their height and women tend to under-estimate their weight. So relying heavily on memory or self-report, which can be more common in a retrospective approach through necessity, can introduce biases (error).

The advantages of a prospective approach is that you have more control over what data are collected and when, and you can control the quality of data collected (so, make sure all the interviewers are well trained and use calibrated equipment or standardized tools). The disadvantages are that it takes A LOT of time and A LOT of money. As we know in public health, grants are typically only for a few years at a time. And a grant of 3-years isn't going to get you very far in studying someone's life course. Some of the most challenging things in life course research are funding, and maintaining interest and momentum over the long haul.

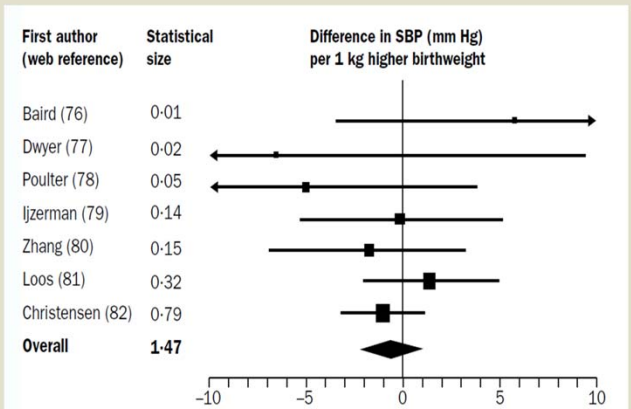


Figure 4: **Association between birthweight and later systolic blood pressure (SBP) in published studies of monozygotic twin pairs**

Conventions as in figure 1, with a diamond indicating the inverse-variance-weighted combined point estimate and 95% CI. All of these regression coefficients were adjusted for current weight (including body-mass index), except for Dwyer et al, which involved adjustment for fat mass.

Huxley, Neil & Collins. Lancet, 2002; 360: 659-665

18

Slide #18:
There are hundreds of studies on the topic of chronic disease development over the life course. One way we can make sense of it all is to look to meta-analyses. A meta-analysis is a study of other people's studies. It is an attempt to bring together all of the available and similar evidence on a topic and to calculate a pooled (or average) number. This is a meta-analysis of studies which looked at the association between birth weight and high blood pressure in later life (taken from the paper shown on slide #19).

This graph is called a forest plot, which is a special kind of graph that you can get in meta-analyses. (1) The list of studies included in the analysis is listed on the left. (2) The number next to the author's name indicates where you can find them in the reference list (#76, 77 etc). (3) The statistical size of each study is listed and is also illustrated by the size of the square (in the graph). Studies with lots of participants tend to have a larger statistical size, are shown using a larger sized box and are given more weight, and studies with smaller numbers of participants tend to have a smaller statistical size, are shown by a smaller box and are given less weight. The weight we give each study is important, it's like the weight given to evidence at a criminal trial. Just as the evidence given in a criminal trial by a law-abiding public health professional may be considered more reliable and trust-worthy than the evidence given by a shady drug dealer, the evidence provided by bigger studies with more participants may be considered to be more reliable and trust-worthy than the evidence provided by smaller studies with fewer participants. (4) The zero line shows the null. A study whose result lies on the zero line found no association between birth weight and high blood pressure, in other words blood pressure was very similar in people with both lower and higher birth weights. (5) The placing of the box relative to the x-axis shows the result of each of the studies (notice numbers of the right side of the x-axis are positive, and numbers to the left are negative), and the lines on either side of the box represent the 95% confidence interval. For example, this study by Poulter found that for every 1 kg increase in birth weight, blood pressure decreased by 5 mmHg (the result is -5 mmHg). And, this study by Baird found the opposite, that for every 1 kg increase in birth weight, blood pressure increased by 6 mmHg (the result is +6 mmHg). The narrower the confidence interval the better, because the width of the confidence intervals indicates how (un)certain we are that the result is where we say it is. (6) The pooled estimate, or average result, when all of these studies are put together, giving more weight to the bigger studies, is shown as a diamond. The diamond is like a magnet, and it is drawn more powerfully towards the results from the bigger studies (the bigger boxes on the graph). The pooled result of this meta-analysis therefore is that for every 1 kg increase in birth weight, blood pressure reduced by 0.6 mmHg.

Forest plots and meta-analyses are useful because instead of having to take hours to read each individual study and then try to piece it together ourselves, we can quickly look at the graph and in 30 seconds know what the spread of data is across all of the different studies, how much confidence we have in the data, and what the pooled result is.

ARTICLES

Articles

Unravelling the fetal origins hypothesis: is there really an inverse association between birthweight and subsequent blood pressure?

Rachel Huxley, Andrew Neil, Rory Collins

Summary

Background The association between birthweight and subsequent blood pressure levels has been considered to provide some of the strongest, and most consistent, support for the "fetal origins" hypothesis of adult disease. It had been estimated that a 1 kg higher birthweight is typically associated with a 2–4 mm Hg lower systolic blood pressure.

Methods 55 studies that had reported regression coefficients of systolic blood pressure on birthweight (with 48 further studies that reported only the direction of this association), and seven such studies within twin pairs, were identified. Each study was weighted according to the inverse of the variance of the regression coefficient (ie, "statistical size"), and combined using a "fixed effects" approach.

Findings Among the 55 studies that reported regression coefficients, there was a clear trend (p<0·0001) towards weaker associations in the larger studies: −1·9 mm Hg/kg in those with less than about 1000 participants; −1·5 mm Hg/kg with about 1000–3000 participants; and −0·6 mm Hg/kg with more than 3000 participants. By contrast with the inverse associations reported in 52 of these 55 studies, only 25 of the 48 studies that did not report regression coefficients found an inverse association (p<0·0001 for heterogeneity). Almost all of these regression coefficients had been adjusted for current weight (whereas few were adjusted for potential confounding factors), and removal of this adjustment in the larger studies reduced the estimated association to −0·4 mm Hg/kg. For studies within monozygotic twin pairs, the combined estimate was −0·6 mm Hg/kg with adjustment for current weight, and was also reduced without this adjustment.

Interpretation Claims of a strong inverse association between birthweight and subsequent blood pressure may chiefly reflect the impact of random error, selective emphasis of particular results, and inappropriate adjustment for current weight and for confounding factors. These findings suggest that birthweight is of little relevance to blood pressure levels in later life.

Lancet 2002; **360:** 659–65

Introduction

One of the original stimuli for the "fetal origins" hypothesis of adult disease was the observation that areas of Britain with the highest rates of neonatal mortality (and, by inference, of impaired fetal growth) early in the 20th century tended to have the highest rates of coronary heart disease later in the century.[1] Subsequently, many retrospective studies have investigated associations of birthweight and of various other birth-related measures (such as placental to birthweight ratio, ponderal index, abdominal and head circumference) with vascular disease risk factors and disease in later life. Birthweight has been the most widely studied measure in such retrospective studies (chiefly due to its availability from existing records or personal recall), and the evidence for an association of adverse outcomes with lower birthweight is considered to be strongest for blood pressure.[2,3]

Based on review of multivariate regression coefficients from 28 studies reported by March 1996, involving a total of 15 000 people, it was previously estimated that a 1 kg higher birthweight is typically associated with a 2–4 mm Hg lower systolic blood pressure.[4] A recent update of that review,[5] which included regression coefficients from an additional 27 studies, involving over 367 000 people, continued to suggest an inverse association of −2 mm Hg/kg (as did another recent review of the same studies[6]). But studies that had not reported the regression coefficient for this association did not contribute to those quantitative estimates, and no allowance was made for the size of the contributing studies. Moreover, whereas almost all of the available regression coefficients had been adjusted for measures of current weight when blood pressure was assessed, few involved adjustment for other potential confounding factors. The purpose of the present paper is to explore the possible impact of these issues, and so determine the likely relevance of birthweight to subsequent blood pressure.

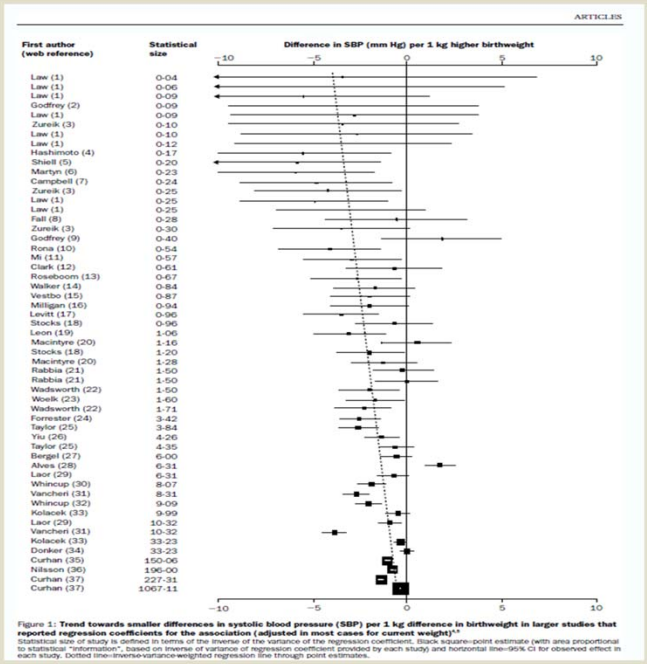
Methods

Studies reporting by March 2000 on the association between birthweight and subsequent blood pressure had been identified previously for two systematic reviews of the available literature.[4,5] Details of the search strategies for such studies, and the inclusion and exclusion criteria, are provided in those reviews. There were 55 eligible studies (ie, individual cohorts, or subsets analysed separately) that had reported regression

19

Slide #19:

Now to publication bias. The scientific media is very like the news media. And, just as the news media hates to report that today had normal weather, everyone got up and went to work as usual and everyone was nice to one another, the medical media hates to report its equivalent of null findings or pokey-small findings. There is nothing more the medical media loves than studies with huge, extreme findings, studies that think they have proved everyone else's theory wrong, and when 2 scientists have a veritable fencing match between issues. As such, the studies that tend to get published are ones with positive (exciting) findings. The studies that show there is no difference between groups or no change over time tend to be rejected, and we never know about them. This is an example of publication bias. And, its result is that when we conduct meta-analyses, we tend to over-estimate what the truth might be because more often than not it's the more extreme results that get published. This paper by Huxley, found evidence of publication bias when looking at studies of the effect of birth weight on hypertension in later life.

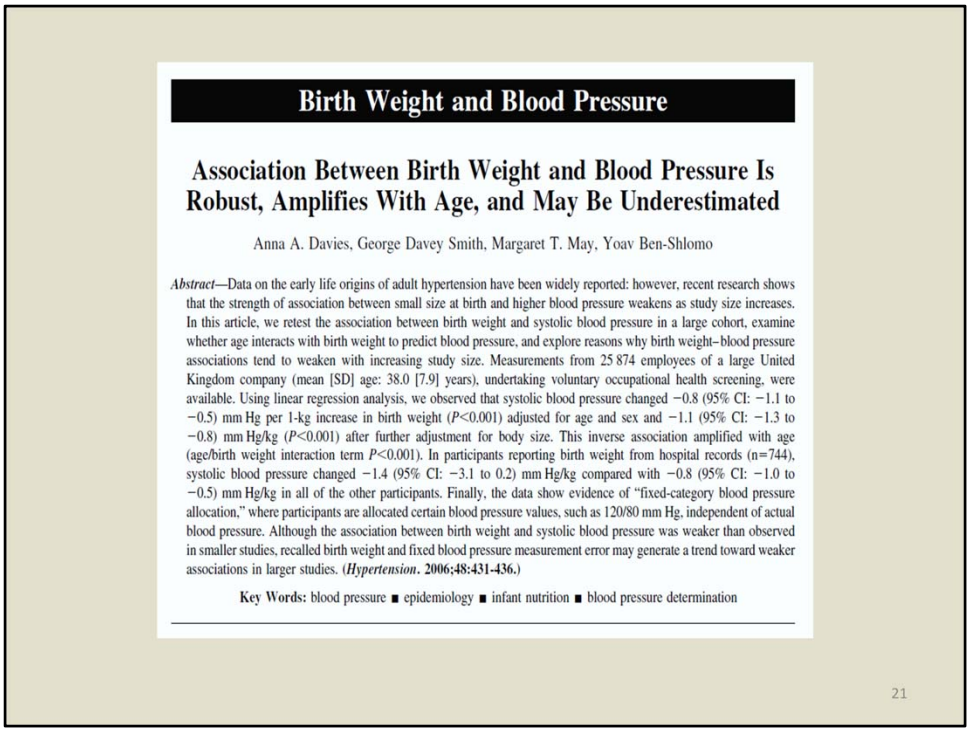


Huxley, Neil & Collins. Lancet, 2002; 360: 659-665

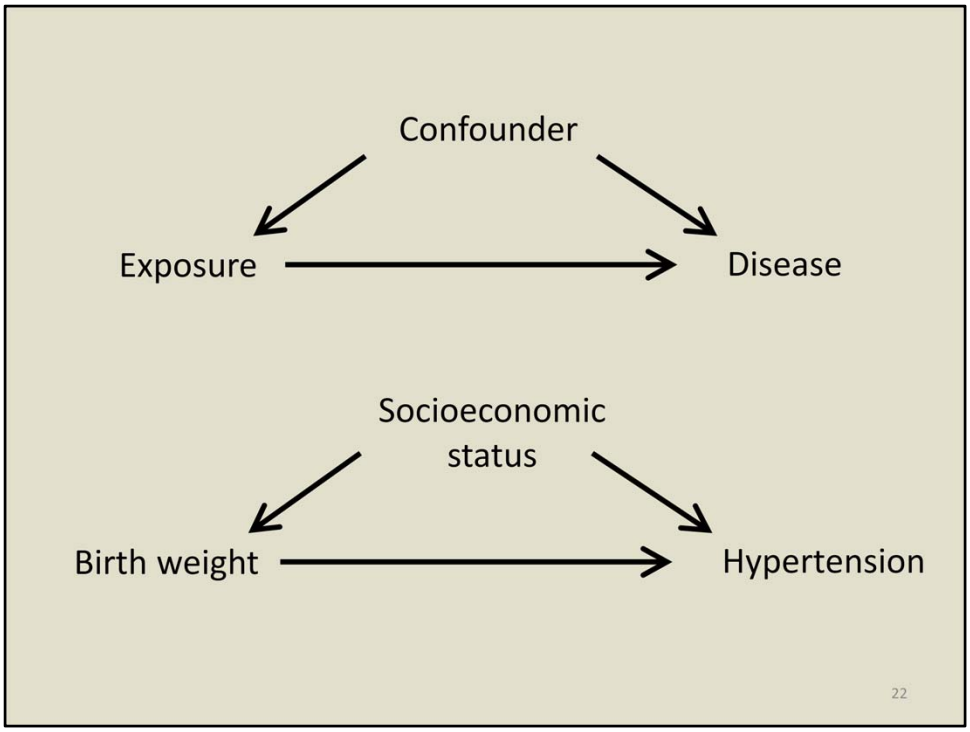
Slide #20:

This is another forest plot from the 2002 Huxley paper. I know the size of the text is small, but we are looking more at the overall pattern than the individual pieces. And, the pattern we see here is that while most of the study results (the boxes) lie on the negative size of the x-axis (so as birth weight increases blood pressure decreases, which is consistent with lower birth weight babies having greater risk of higher blood pressure in later life), the bigger studies shown by the bigger boxes tend to have results closer to the null line and the smaller studies tend to have more extreme values. Per the authors this shows the results from smaller studies are more likely to be published when extreme, which is publication bias. As such, the true association between birth weight and blood pressure in later life is likely to be weaker than we had first thought. Taking all of these studies together, the pooled result suggested that for every 1 kg increase in birth weight, blood pressure decreased by 0.6 mmHg. Previous estimates had suggested that it was higher than this, between 2 and 4 mmHg. This means that while lower birth weight babies may be at increased risk of higher blood pressure in later life compared to normal weight babies, it is by only a small amount.

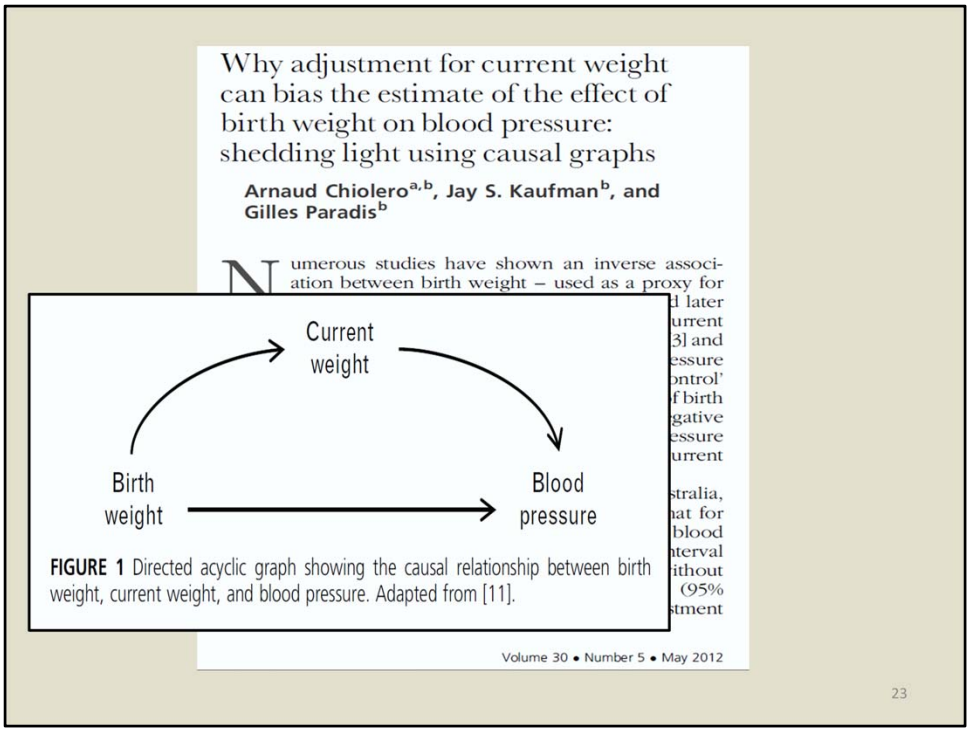
To put this number in perspective, the average (healthy) blood pressure is 120/80 and hypertension is when your blood pressure is 140/90 or more. As such, the 0.6 mmHg in itself while statistically significant, is unlikely to be clinically significant. What some authors say this means is that if we wanted to reduce blood pressure in a population, putting all of our money into preventing low birth weight might not help much. However, what others say is that birth weight in itself is not what we are looking at per se. It is what birth weight represents, the sub-optimal environment in pregnancy and birth weight is only a proxy, and many of these factors combine over the life course to have larger effects.



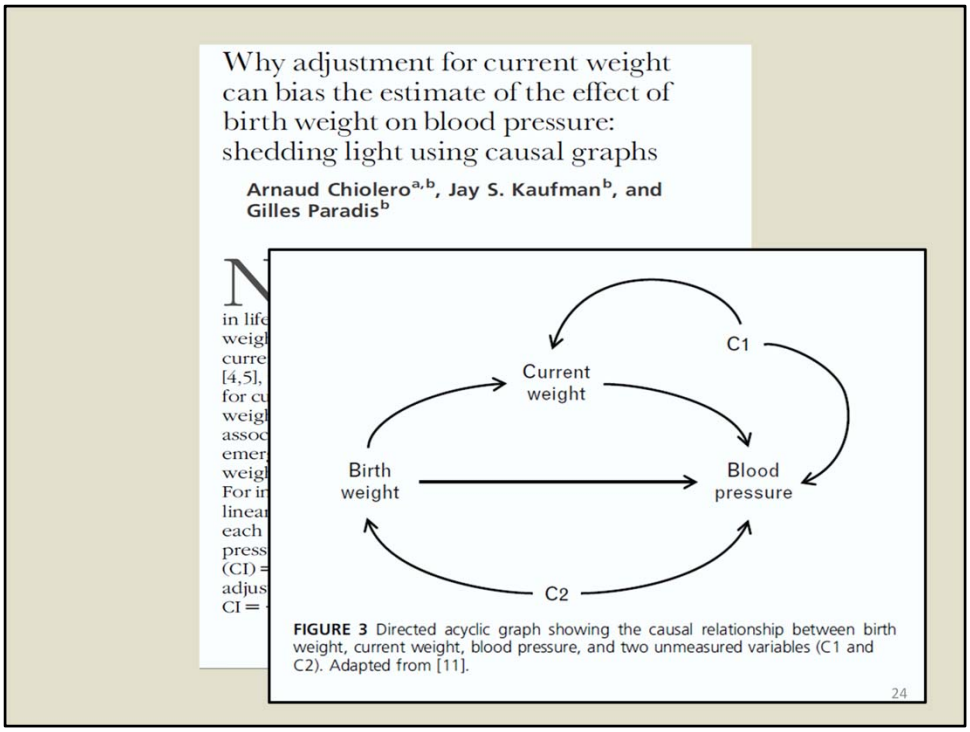
Slide #21:
Indeed, this paper while also finding that the relationship between birth weight and hypertension was perhaps less than previously thought (in agreement with the Huxley paper), they found that the effect of birth weight on blood pressure increased as we get older, which could support this theory. These authors also suggest that as well as publication bias, another reason why larger studies may have smaller effects is because they often rely on self-reported birth weight (people's memories) instead of using hospital records. As such, measurement error could be playing a part.



Slide #22:
Another methodological consideration raised in this and other papers, is that many studies in life course research have failed to adequately adjust for confounding factors. A confounding factor in this context could be something that can explain a relationship between an exposure and a disease like that between birth weight and hypertension. An example of a confounding factor in the association between birth weight and hypertension is socioeconomic status. Babies born to parents of lower socioeconomic status more likely to have lower birth weight and people of lower socioeconomic status more likely to have poorer diets and exercise less which leads to hypertension. As such, if we fail to take socioeconomic status into account in our studies, our results may be over-inflated (falsely high). Some of the confounders, though, like socioeconomic status are hard to completely adjust for, and even if studies have tried to do this, there can still be what is called residual confounding. This is because, socioeconomic status and factors like it are so pervasive, they get into all parts of our lives and experiences and are hard to fully take out of the equation.



Slide #23:
Moving on now from adjusting for confounders to adjusting for causal factors or intermediates, there is still much debate in life course research about whether studies should include adjustment for current body size or weight. Current weight is a causal factor in the relationship between birth weight and blood pressure because birth weight is positively associated with current weight and current weight is a determinant of blood pressure. The reason many researchers have adjusted these types of analyses for current weight is that they are trying to get at the effect of birth weight on blood pressure that is <u>not</u> mediated through current weight (an unbiased estimate of the direct effect). However, given the association between birth weight and blood pressure is more likely to look like this ….



Slide #24:

… with many more variables like physical activity (C1 in this diagram) and potential maternal or genetic factors (C2 in this diagram) in the mix, adjusting for current weight might not give us an unbiased estimate of the direct effect of birth weight on blood pressure. The estimate could be biased by the effects of variables like C1, called colliders. And, in the relationship between early life and childhood exposures with chronic disease in later life, there are probably lots of potential colliders.

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Practice of Epidemiology

On the Pitfalls of Adjusting for Gestational Age at Birth

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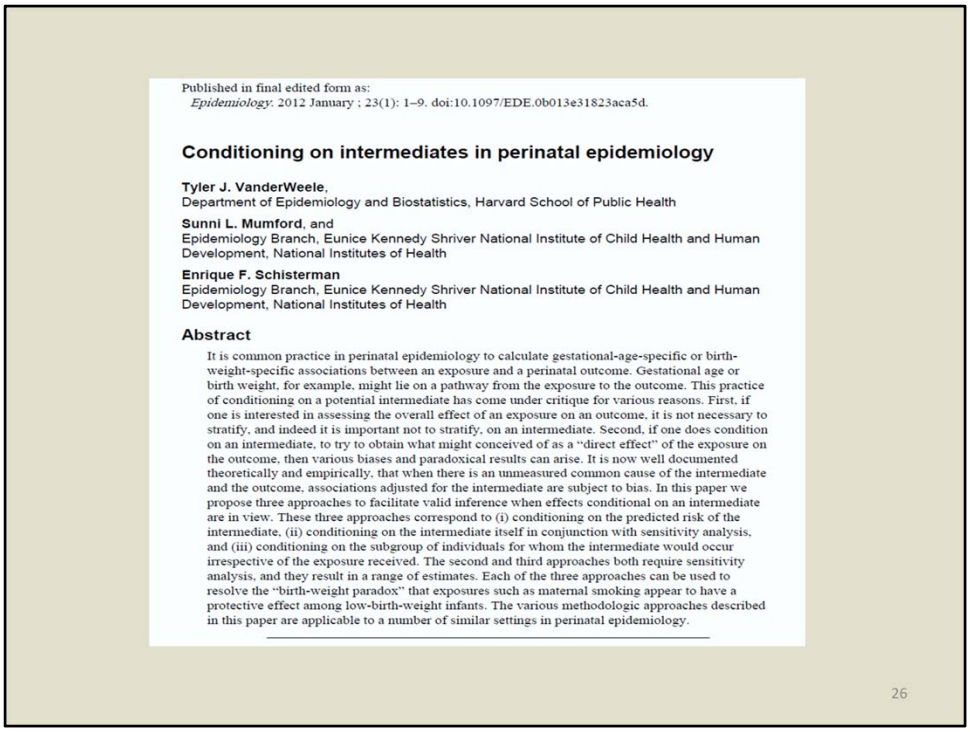
Preterm delivery is a powerful predictor of newborn morbidity and mortality. Such problems are due to not only immaturity but also the pathologic factors (such as infection) that cause early delivery. The understanding of these underlying pathologic factors is incomplete at best. To the extent that unmeasured pathologies triggering preterm delivery also directly harm the fetus, they will confound the association of early delivery with neonatal outcomes. This, in turn, complicates studies of newborn outcomes more generally. When investigators analyze the association of risk factors with neonatal outcomes, adjustment for gestational age as a mediating variable will lead to bias. In the language of directed acyclic graphs, gestational age is a collider. The theoretical basis for colliders has been well described, and gestational age has recently been acknowledged as a possible collider. However, the impact of this problem, as well as its implications for perinatal research, has not been fully appreciated. The authors discuss the evidence for confounding and present simulations to explore how much bias is produced by adjustments for gestational age when estimating direct effects. Under plausible conditions, frank reversal of exposure-outcome associations can occur. When the purpose is causal inference, there are few settings in which adjustment for gestational age can be justified.

adjustment; collider; directed acyclic graph; gestational age; infant mortality; mediating variable; premature birth; stratification

25

Slide #25:
Following on from current weight, several papers have also raised the issue of whether or not we should be adjusting for gestational age. As we know, gestational age has a direct effect on birth weight, and if we induce labor early in every pregnant woman, say at 37 weeks, we could lower birth weight. However, our understanding of what causes a woman to go into labor (and thus determine gestational age) is patchy at best. And what this paper ….



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Conditioning on intermediates in perinatal epidemiology

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Abstract

It is common practice in perinatal epidemiology to calculate gestational-age-specific or birth-weight-specific associations between an exposure and a perinatal outcome. Gestational age or birth weight, for example, might lie on a pathway from the exposure to the outcome. This practice of conditioning on a potential intermediate has come under critique for various reasons. First, if one is interested in assessing the overall effect of an exposure on an outcome, it is not necessary to stratify, and indeed it is important not to stratify, on an intermediate. Second, if one does condition on an intermediate, to try to obtain what might conceived of as a "direct effect" of the exposure on the outcome, then various biases and paradoxical results can arise. It is now well documented theoretically and empirically, that when there is an unmeasured common cause of the intermediate and the outcome, associations adjusted for the intermediate are subject to bias. In this paper we propose three approaches to facilitate valid inference when effects conditional on an intermediate are in view. These three approaches correspond to (i) conditioning on the predicted risk of the intermediate, (ii) conditioning on the intermediate itself in conjunction with sensitivity analysis, and (iii) conditioning on the subgroup of individuals for whom the intermediate would occur irrespective of the exposure received. The second and third approaches both require sensitivity analysis, and they result in a range of estimates. Each of the three approaches can be used to resolve the "birth-weight paradox" that exposures such as maternal smoking appear to have a protective effect among low-birth-weight infants. The various methodologic approaches described in this paper are applicable to a number of similar settings in perinatal epidemiology.

Slide #26:
… and this paper suggest is that gestational age may be on the causal pathway between exposure and outcome, and/or be a collider. If there is a common cause of both gestational age (when labor is triggered) and our outcome (chronic disease), then by adjusting for gestational age we could be introducing bias. Now, I don't claim to know any of the answers to this, it is at this point that I would want to consult my friendly neighborhood statistician, but these authors have at least got me thinking and asking the question.

Summarizing the methodological and statistical issues we have discussed before we go on, while we don't want to throw the baby out with the bath water, we need to be savvy and think about the bigger picture. We need to consider how publication bias might be impacting our results, how measurement error may be at play (self-reported data vs hospital records), whether studies have adjusted for confounders, and how they have handled factors like current weight on the causal pathway. Finally, we need to consider how we handle gestational age.

Slide #27:
Practical applications of life course research. Given all we have heard about critical and sensitive periods in development, one time when we have direct control over exposures (the environment) is in IVF, in vitro fertilization.

Slide #28:
Louise Brown was the first baby born using IVF in 1978. Since then, 5 million babies have been born using IVF, and most of us here in this room probably know someone who has used it. IVF was pioneered by Robert Edwards and he won a Nobel Prize for this work in 2010, shortly before he died. In June, I attended an OB/GYN talk at OHSU on the Barker Hypothesis (so taking a life course perspective) and IVF. Given that the oldest person born using IVF was born in 1978 (so is about 34 years old), there are limited long term data. However, with the increasing numbers of children born using this technique, it is an important and growing area of research.

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Review

Preterm birth and low birth weight among *in vitro* fertilization singletons: A systematic review and meta-analyses

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ABSTRACT

Our objective was to determine the risks of preterm birth (PTB) and low birth weight (LBW) in singletons conceived through *in vitro* fertilization (IVF) ± intracytoplasmic sperm injection (ICSI) compared to spontaneously conceived singletons after matching or controlling for at least maternal age. The MOOSE guidelines for meta-analysis of observational studies were followed. Medline and Embase were searched using comprehensive search strategies. Bibliographies of identified articles were reviewed. English language studies examining LBW or PTB in singletons conceived by IVF or IVF/intracytoplasmic sperm injection, compared with spontaneously conceived singletons, that matched or controlled for at least maternal age. Two reviewers independently assessed titles, abstracts, full articles and study quality and extracted data. Dichotomous data were meta-analyzed using relative risks (RR) as measures of effect size with a random effects model and for continuous data weighted mean difference was calculated. Seventeen studies were included with 31,032 singletons conceived through IVF (±ICSI) and 81,119 spontaneously conceived singletons. After matching or controlling for maternal age and often other factors, compared to spontaneously conceived singletons, IVF singletons had increased risks of our two primary outcomes, PTB (RR 1.84, 95% CI 1.54, 2.21) and LBW (<2500 g, RR 1.60, 95% CI 1.29, 1.98). Singletons conceived through IVF or IVF/ICSI were at increased risk for late PTB (32–36 weeks, RR 1.52, 95% CI 1.01, 2.30), moderate PTB <32–33 weeks (RR 2.27, 95% CI 1.73, 2.97), very LBW (<1500 g, RR 2.65, 95% CI 1.83, 3.84), and intrauterine growth restriction (RR 1.45, 95% CI 1.04, 2.00), lower birth weights (−97 g, 95% CI −161 g, −33 g) and shorter mean gestations (−0.6 weeks, 95% CI −0.9 weeks, −0.4 weeks). In conclusion, IVF singletons have significantly increased risks of PTB, LBW and other adverse perinatal outcomes compared to spontaneously conceived singletons after matching or controlling for maternal age at least.

29

Slide #29:
Babies born using IVF appear to be at higher risk of pre-term birth and low birth weight.

REPRODUCTION-DEVELOPMENT

Impaired Placental Nutrient Transport in Mice Generated by *in Vitro* Fertilization

Enrrico Bloise, Wingka Lin, Xiaowei Liu, Rhodel Simbulan, Kevin S. Kolahi, Felice Petraglia, Emin Maltepe, Annemarie Donjacour, and Paolo Rinaudo

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More than 4.5 million children have been conceived by *in vitro* fertilization (IVF). Interestingly, singleton IVF offspring born at term have an increased incidence of low birth weight. The mechanism responsible for the lower birth weight is unknown, but alterations in placental function are possible. Hence, the goal of our study was to examine placental growth and function in mice generated *in vivo* or *in vitro*. To assess placental function, blastocysts were generated by IVF or produced by natural mating (control group); both IVF and control blastocysts were transferred to pseudopregnant recipients. Placental weights did not differ at embryonic d 15.5 (E15.5) but were increased at E18.5 in the IVF group (25.4%, $P < 0.001$) compared with control. Proliferation was increased in IVF placentae, whereas overall placental gross morphology and apoptosis were not affected. Both fetal weights (16.4% lower at E15.5 and 8.8% lower at E18.5, $P < 0.05$) and fetal to placental ratios were lower ($P < 0.001$) in the IVF compared with the control group at both time points, whereas birth weights did not differ. At E18.5, the mRNA for selected glucose, system A amino acid transporters, and imprinted genes were down-regulated in IVF placentae. GLUT3 protein level was decreased in the IVF group ($P < 0.05$). Importantly, intrajugular injections of ^{14}C-methyl-D-glucose or ^{14}C-MeAIB tracers (n = 6 litters per group) showed that placental transport of glucose and amino acids were 24.8% (not significant) and 58.1% ($P < 0.05$) lower in the IVF group. Fetal accumulation of glucose was not different, but amino acid accumulation was significantly (36 %) lower in IVF fetuses ($P < 0.05$). We conclude that IVF alters both fetal and placental growth and, importantly, decreases placental transport efficiency in mice conceived by IVF. (***Endocrinology*** **153: 3457–3467, 2012)**

30

Slide #30:
One suggestion is that this appears to be mediated through changes in the placenta. According to this study, IVF placenta may have down-regulated glucose and amino acid transporters, and reduced glucose and amino acid transport efficiency across the placenta from mother to fetus.

Growth and development of children born after in vitro fertilization

Manon Ceelen, M.Sc.,[a] *Mirjam M. van Weissenbruch, M.D., Ph.D.,*[a] *Jan P. W. Vermeiden, Ph.D.,*[b] *Flora E. van Leeuwen, Ph.D.,*[c] *and Henriette A. Delemarre-van de Waal, M.D., Ph.D.*[a]

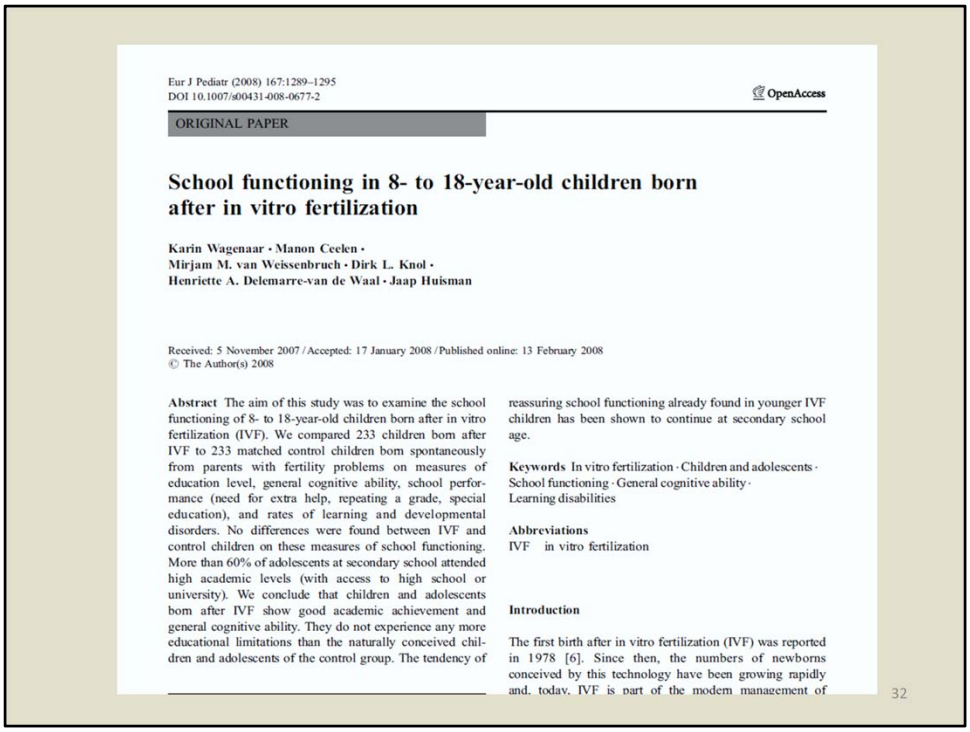
[a] Department of Paediatrics, Institute for Clinical and Experimental Neuroscience, [b] Department of Obstetrics and Gynaecology, VU University Medical Center; and [c] Department of Epidemiology, Netherlands Cancer Institute, Amsterdam, The Netherlands

Objective: To evaluate growth and development of children born after IVF treatment.
Design: Literature review.
Conclusion(s): At present there is substantial evidence that children born after IVF are at increased risk for adverse perinatal outcome, congenital malformations, and rare epigenetic defects. It is still unclear whether observed health problems originate from the IVF procedure itself or the underlying subfertility problems of the parents. Current follow-up studies regarding postnatal growth and morbidity rates are scarce with conflicting results and other areas of long-term research in children born after IVF are still in its infancy. The importance of the worldwide continuing monitoring of children born after IVF to investigate potential long-term consequences including the development of cardiovascular diseases is therefore highlighted. (Fertil Steril® 2008;90:1662–73. ©2008 by American Society for Reproductive Medicine.)

Key Words: Epigenetic defects, follow-up research, in vitro fertilization, perinatal outcome, postnatal development

31

Slide #31:
Growth in childhood seems to be largely unaffected. The studies reviewed here of children up to age 13 years, found no major pathological features in growth and physical development.



Eur J Pediatr (2008) 167:1289–1295
DOI 10.1007/s00431-008-0677-2

OpenAccess

ORIGINAL PAPER

School functioning in 8- to 18-year-old children born after in vitro fertilization

Karin Wagenaar · Manon Ceelen · Mirjam M. van Weissenbruch · Dirk L. Knol · Henriette A. Delemarre-van de Waal · Jaap Huisman

Received: 5 November 2007 / Accepted: 17 January 2008 / Published online: 13 February 2008

Abstract The aim of this study was to examine the school functioning of 8- to 18-year-old children born after in vitro fertilization (IVF). We compared 233 children born after IVF to 233 matched control children born spontaneously from parents with fertility problems on measures of education level, general cognitive ability, school performance (need for extra help, repeating a grade, special education), and rates of learning and developmental disorders. No differences were found between IVF and control children on these measures of school functioning. More than 60% of adolescents at secondary school attended high academic levels (with access to high school or university). We conclude that children and adolescents born after IVF show good academic achievement and general cognitive ability. They do not experience any more educational limitations than the naturally conceived children and adolescents of the control group. The tendency of reassuring school functioning already found in younger IVF children has been shown to continue at secondary school age.

Keywords In vitro fertilization · Children and adolescents · School functioning · General cognitive ability · Learning disabilities

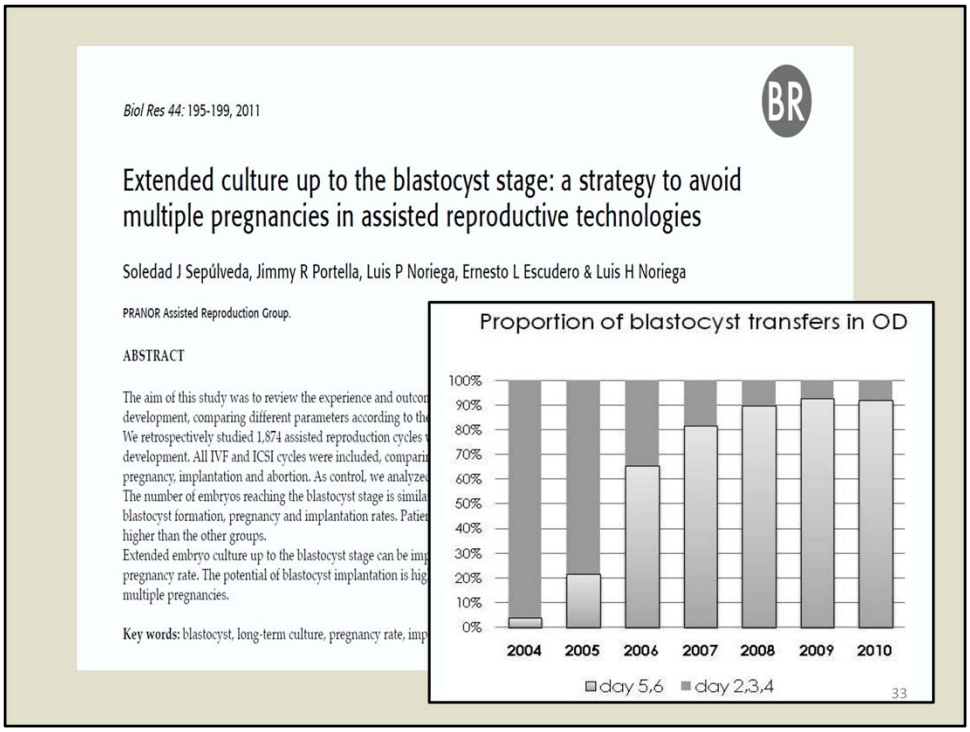
Abbreviations
IVF in vitro fertilization

Introduction

The first birth after in vitro fertilization (IVF) was reported in 1978 [6]. Since then, the numbers of newborns conceived by this technology have been growing rapidly and, today, IVF is part of the modern management of

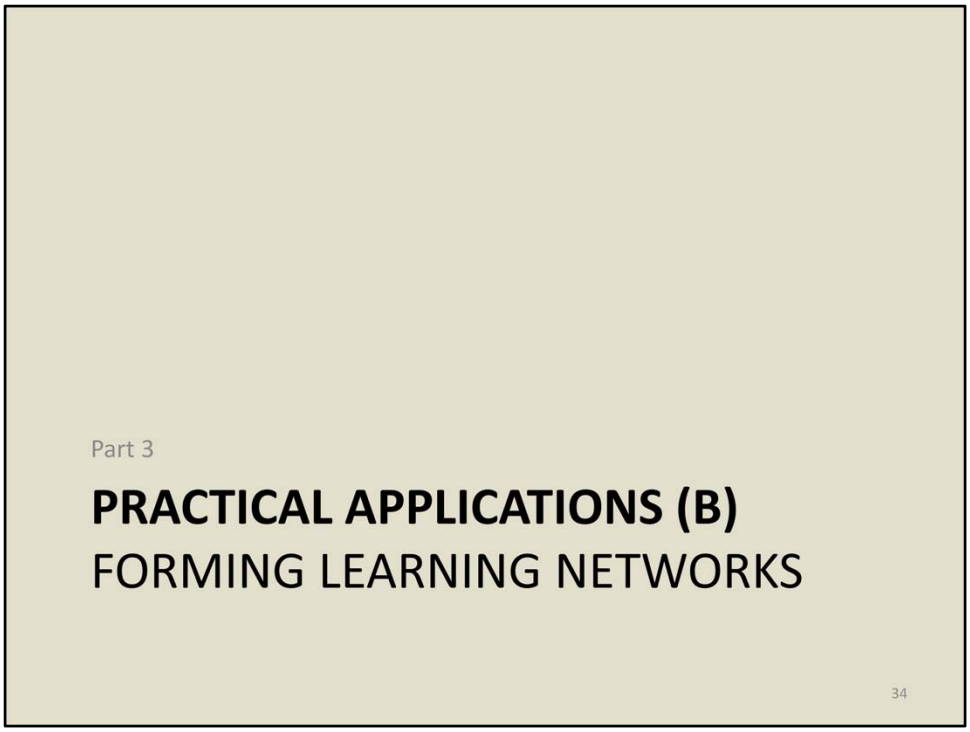
32

Slide #32:
In addition, this study although very small, was reassuring in that it found no difference in the cognitive ability or school performance of 8 and 18 year old children born using IVF compared to children born spontaneously to parents with fertility problems.



Slide #33:
Finally, it is important to consider the changes in IVF techniques over time and the potential implications of keeping embryos in an artificial environment for longer. This graph, shows the percentage of IVF cycles where embryos were implanted at 5-6 days after fertilization compared to 2-4 days. The percentage of embryos implanted at 5-6 days has grown from 4% in 2004 to 90% in 2010, at least at the clinic in this study. I raise this issue because one could hypothesize that the longer we are manipulating the environment of an embryo during these critical periods, the more likely we are to influence development.

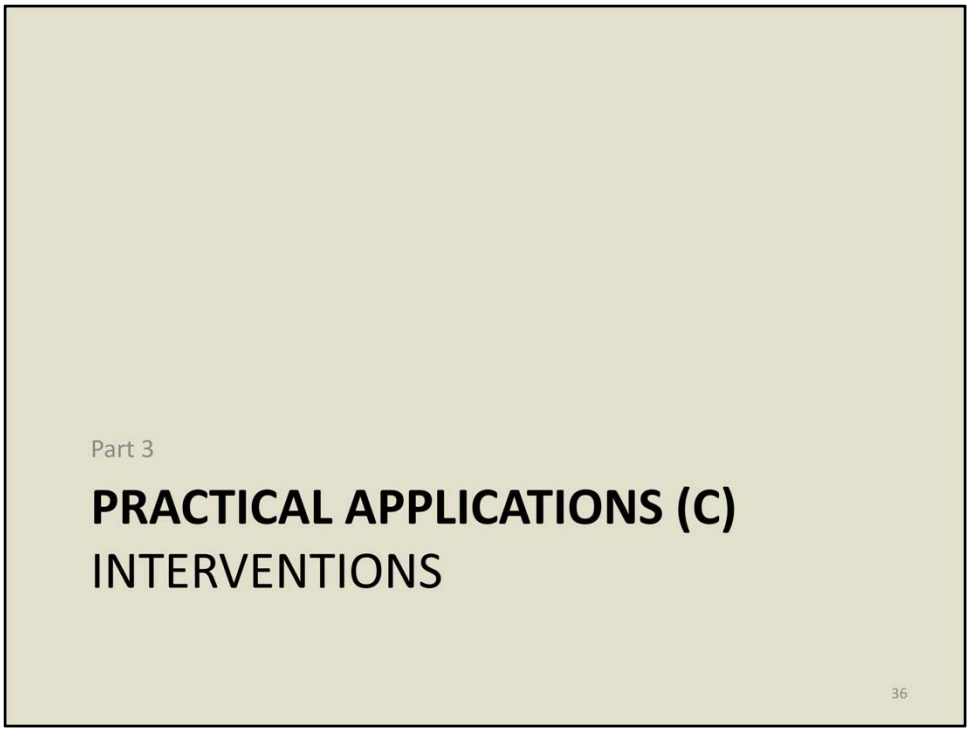
(The OD in the graph stands for oocyte donation)



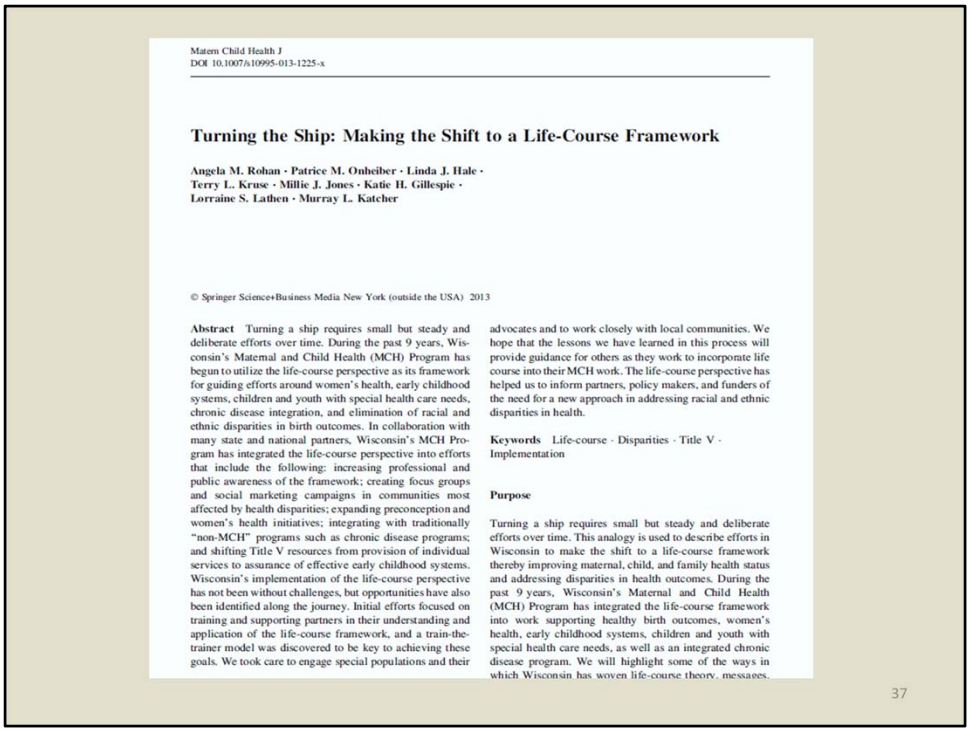
Slide #34:
Another application of this research, is similar to what we are doing here …

Slide #35:

… forming a learning network of people from different disciplines who are interested in this work to expand our understanding, and network and collaborate on research and interventions. This is the web site of the Maternal and Child Health Life Course Network based at UCLA. If you remember the grant we were talking about applying for a while ago to support the formation of a network, this is the group that won it in 2010.



Slide #36:
Finally, to interventions.



Matern Child Health J
DOI 10.1007/s10995-013-1225-x

Turning the Ship: Making the Shift to a Life-Course Framework

Angela M. Rohan · Patrice M. Onheiber · Linda J. Hale · Terry L. Kruse · Millie J. Jones · Katie H. Gillespie · Lorraine S. Lathen · Murray L. Katcher

Abstract Turning a ship requires small but steady and deliberate efforts over time. During the past 9 years, Wisconsin's Maternal and Child Health (MCH) Program has begun to utilize the life-course perspective as its framework for guiding efforts around women's health, early childhood systems, children and youth with special health care needs, chronic disease integration, and elimination of racial and ethnic disparities in birth outcomes. In collaboration with many state and national partners, Wisconsin's MCH Program has integrated the life-course perspective into efforts that include the following: increasing professional and public awareness of the framework; creating focus groups and social marketing campaigns in communities most affected by health disparities; expanding preconception and women's health initiatives; integrating with traditionally "non-MCH" programs such as chronic disease programs; and shifting Title V resources from provision of individual services to assurance of effective early childhood systems. Wisconsin's implementation of the life-course perspective has not been without challenges, but opportunities have also been identified along the journey. Initial efforts focused on training and supporting partners in their understanding and application of the life-course framework, and a train-the-trainer model was discovered to be key to achieving these goals. We took care to engage special populations and their advocates and to work closely with local communities. We hope that the lessons we have learned in this process will provide guidance for others as they work to incorporate life course into their MCH work. The life-course perspective has helped us to inform partners, policy makers, and funders of the need for a new approach in addressing racial and ethnic disparities in health.

Keywords Life-course · Disparities · Title V · Implementation

Purpose

Turning a ship requires small but steady and deliberate efforts over time. This analogy is used to describe efforts in Wisconsin to make the shift to a life-course framework thereby improving maternal, child, and family health status and addressing disparities in health outcomes. During the past 9 years, Wisconsin's Maternal and Child Health (MCH) Program has integrated the life-course framework into work supporting healthy birth outcomes, women's health, early childhood systems, children and youth with special health care needs, as well as an integrated chronic disease program. We will highlight some of the ways in which Wisconsin has woven life-course theory, messages,

37

Slide #37:
One example is from Wisconsin's Maternal and Child Health Program, published this year. They have been using a life course framework to guide their approach to reducing racial and ethnic health disparities for 9 years, collaborating with many state and national partners. Their 3 inter-related strategies included (1) increase the knowledge base, (2) translate life course theory into a social strategy of programs and policies, (3) build political will and buy-in among a broader base of stakeholders. Their efforts included increasing professional and public awareness of the topic, creating focus groups and social marketing campaigns in communities most affected by health disparities, expanding pre-conception and women's health initiatives, integrating with traditionally "non-MCH" programs such as chronic disease, and by moving their title 5 resources from providing of individual services to providing early childhood systems.

Their project (and paper) is very detailed so I can't do it justice here, but of note they asked African American participants of focus groups to talk about their life course before and after they had children and grandchildren. Moreover, they had Community Advisory Boards to ensure the project was community-driven, and national life course experts were consulted through members of the technical advisory group. And they collaborated with Medicaid and Managed Care Organizations to establish a maternity medical home pilot. Some of their lessons learned speak to how uncomfortable some of their traditional health partners were

with taking on underlying determinants of health outside of their realm of control like racism or community economic development. They also speak to how challenging it is figuring out how to evaluate this broad scope of work.

Matern Child Health J
DOI 10.1007/s10995-013-1271-4

Wisconsin's Lifecourse Initiative for Healthy Families: Application of the Maternal and Child Health Life Course Perspective Through a Regional Funding Initiative

Catherine A. Frey · Philip M. Farrell · Quinton D. Cotton · Lorraine S. Lathen · Katherine Marks

Abstract National experts are calling for more integrated approaches such as the life course perspective to reduce health disparities and achieve greater health equity. The translation and application of the life course perspective is therefore of great interest to public health planners, policy makers and funders to promote community-wide improvements in maternal and child health. However, few organizations have applied the life course perspective in designing strategic funding initiatives. For over three decades, Wisconsin has observed persistent racial disparities in birth outcomes. This complex public health issue led to the development of the Lifecourse Initiative for Health Families, a regional multi-million dollar funding initiative created and supported by the Wisconsin Partnership Program of the University of Wisconsin School of Medicine and Public Health (Created by the UW SMPH from an endowment following the conversion of Blue Cross Blue Shield United of Wisconsin, the Partnership Program makes investments in research, education, and public health and prevention initiatives that improve health and reduce health disparities in the state.). Over a 2-year period, the program funded four collaboratives to adopt a life course perspective and develop strategic plans for improving African American birth outcomes. The Twelve-point plan to close the black–white gap in birth outcomes provided the framework for the planning process. Despite the conceptual challenges, the life course perspective was embraced by the collaboratives, challenged community assumptions on the root causes of poor birth outcomes and provided a unifying funding construct for organizing and planning complementary individual-level interventions with social and physical environmental change strategies. These integrated and complimentary approaches provide a long-term opportunity to address the persistent racial birth outcome disparity in Wisconsin.

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38

Slide # 38:
The second paper goes into more depth about their Life Course Initiative for Healthy Families. The funding initiative was created and supported by the University of Wisconsin's School of Medicine and Public Health. They engaged non-traditional partners including faith-based groups and the YMCA. Some of the tools they used were the *Unnatural Causes* videos and Robert Wood Johnson's *Social Determinants: A New Way of Talking*.

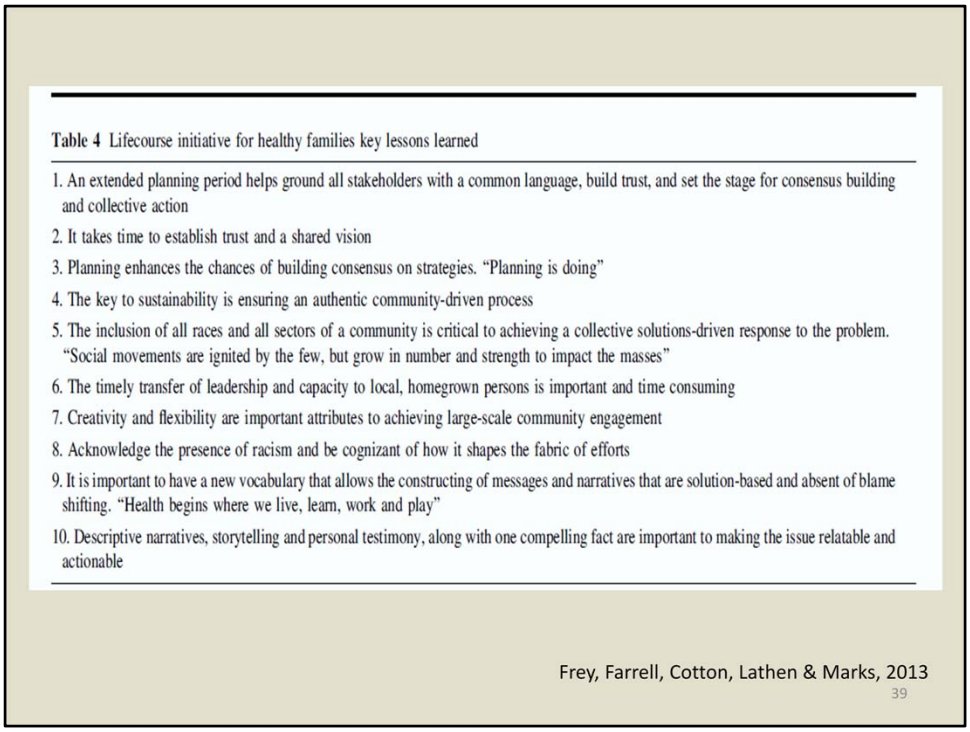

Table 4 Lifecourse initiative for healthy families key lessons learned

1. An extended planning period helps ground all stakeholders with a common language, build trust, and set the stage for consensus building and collective action
2. It takes time to establish trust and a shared vision
3. Planning enhances the chances of building consensus on strategies. "Planning is doing"
4. The key to sustainability is ensuring an authentic community-driven process
5. The inclusion of all races and all sectors of a community is critical to achieving a collective solutions-driven response to the problem. "Social movements are ignited by the few, but grow in number and strength to impact the masses"
6. The timely transfer of leadership and capacity to local, homegrown persons is important and time consuming
7. Creativity and flexibility are important attributes to achieving large-scale community engagement
8. Acknowledge the presence of racism and be cognizant of how it shapes the fabric of efforts
9. It is important to have a new vocabulary that allows the constructing of messages and narratives that are solution-based and absent of blame shifting. "Health begins where we live, learn, work and play"
10. Descriptive narratives, storytelling and personal testimony, along with one compelling fact are important to making the issue relatable and actionable

Frey, Farrell, Cotton, Lathen & Marks, 2013

39

Slide #39:
Some of their take-ways were "planning is doing", make sure there is timely transfer of leadership and capacity to local and home-grown persons, use a new vocabulary and avoid "blame shifting" in messages, and use narratives and stories.

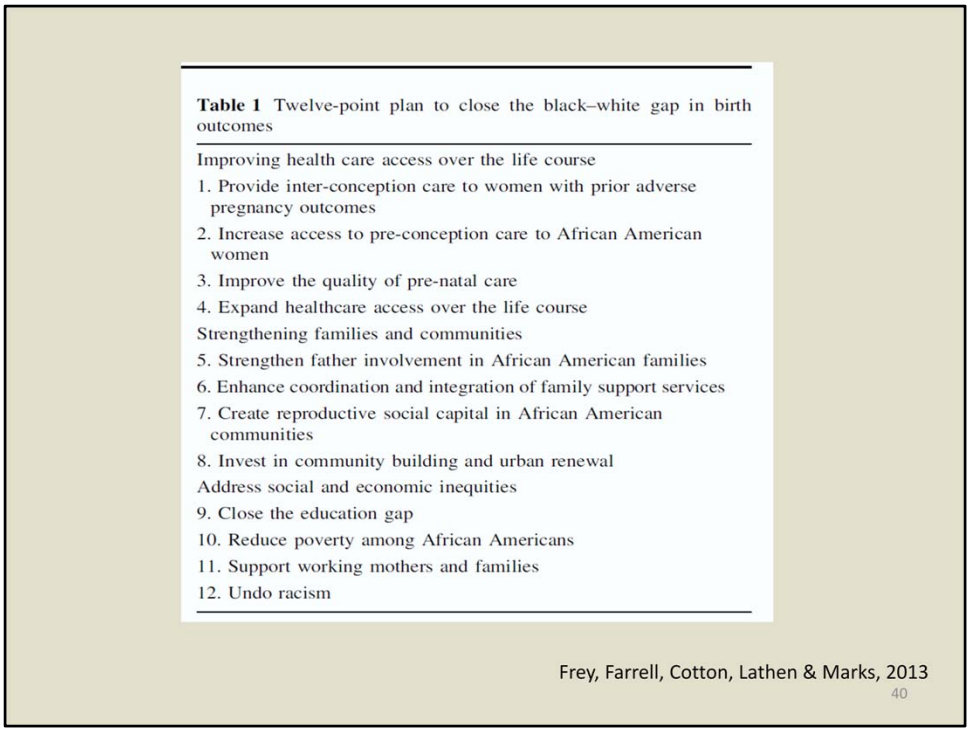

Table 1 Twelve-point plan to close the black–white gap in birth outcomes

Improving health care access over the life course
1. Provide inter-conception care to women with prior adverse pregnancy outcomes
2. Increase access to pre-conception care to African American women
3. Improve the quality of pre-natal care
4. Expand healthcare access over the life course
Strengthening families and communities
5. Strengthen father involvement in African American families
6. Enhance coordination and integration of family support services
7. Create reproductive social capital in African American communities
8. Invest in community building and urban renewal
Address social and economic inequities
9. Close the education gap
10. Reduce poverty among African Americans
11. Support working mothers and families
12. Undo racism

Slide #40:
This is their 12-point plan, which communities used to develop their action plans. It is lofty, and I draw your attention to “undo racism”, “reduce poverty” and “close the education gap”. But, if you are interested I encourage you to read these papers and to contact Wisconsin directly. I am sure there is a lot they could tell you that wasn’t included here.

Wrap-up

- Reminder from Siobhan's and Susan's presentations
  - Critical periods in life and accumulation of risk
  - Multiple layers of factors that influence health status
  - Transgenerational transmission of disease risk
- Methodological considerations
  - Retrospective vs prospective approaches
  - Using meta-analyses to make sense of the literature
  - Publication bias and confounding may over-estimate effect of birth weight on later chronic disease risk
  - Inappropriate adjustment for causal factors/intermediates
- Practical applications of life course research
  - IVF
  - Learning networks
  - Public health interventions

41