

## TOP 10 TOPICS:

- NUTRITION
- PREMATUREITY
- YOUTH HEALTH
- STRESS
- BREASTFEEDING
- AND MUCH MORE...



## CANADIAN EARLY CHILDHOOD DEVELOPMENT RESEARCH HAS GONE... INTERNATIONAL!

BY RICHARD E. TREMBLAY AND MICHEL BOIVIN

This is the 12<sup>th</sup> edition of the Top Ten Bulletin series (started in 2002) to highlight the best recent research publications on early childhood development co-authored by at least one Canadian investigator. The ten papers were selected from 78 papers in high-impact international journals during 2013-14 and were ranked by 18 Canadian clinicians and researchers who were blind to the authors. The papers cover a wide spectrum of ground-breaking research, focusing on premature birth, child mortality, perinatal maternal mortality, obesity, asthma, allergies and brain development. Many of the papers investigate causes leading to these problems, including genetics, epigenetics, poverty, stress during pregnancy and child abuse.

The majority of our experts selected as the most important an article on children's death before age five around the world. The results of this huge international research enterprise funded by the Bill & Melinda Gates Foundation, the Aga Khan University and the Toronto Hospital for Sick Children show the Herculean work needed to substantially reduce that death rate. International experts estimated that a meagre 15% of the 3.1 million children under age five who die annually could be saved, even if the most effective interventions were implemented with 90% coverage.

The striking and somewhat surprising commonality among the ten papers summarized here is their international scope. **If there is any doubt that research on human development is a worldwide playing field, this issue of our Top Ten should help convince – and worry – the sceptics!** For example, only two of the first authors of the ten papers are affiliated with a Canadian university.

Hannah Schreier is one of the two – and a good example of the international scope. Schreier came to Canada from Germany as a high-school exchange student, did her undergraduate work at McGill University and her PhD at University of British Columbia under

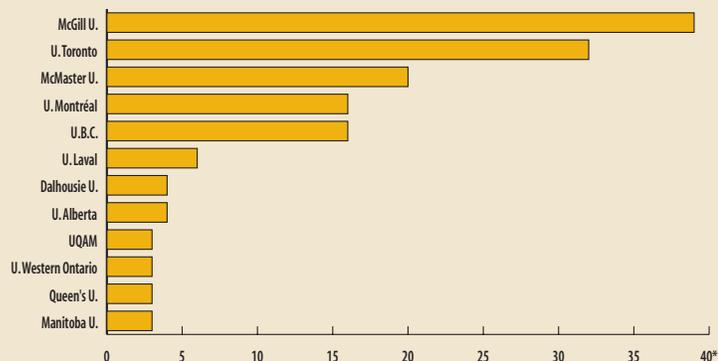
Edith Chen, an American who was Canada Research Chair in Health and Society when the paper was published and who has now moved back to the United States. Their literature review on environmental conditions associated with asthma and obesity (see p. 3) eventually led Schreier to a postdoctoral position in New York and an academic position at Pennsylvania State University. The first authors

of the other eight papers are from England, Germany (2), Pakistan, Scotland, Singapore and the US (2).

Another unexpected and somewhat disturbing outcome of the 2013-14 Top Ten selection is that **none of the studies were done in Canada!** From the eight studies mentioned above, two included Canadian data because they were two of three using national statistics worldwide. The other six publications reported results from data collected in Australia, Belarus, Scotland, Singapore and the US (2). Interestingly, three of these six studies were large birth cohorts from Australia, Belarus and Singapore.

We have never before analysed our Top Ten selection from an international perspective. The surprising results from 2013-14 appear to indicate that investigators in early child development from Canadian universities involved in international studies are the most productive from the perspective of high-impact journal publications. This is likely because the most productive researchers from Canadian universities are those invited to be part of international collaborations. But, the following question remains: **Why are Canadian studies not part of these international collaborations,** at least in 2013-14? We will follow up with a longer-term analysis in our next bulletin. 🦋

## TOP 120 PAPERS (2001-2014)



\* Number of papers with at least one author from a Canadian institution.  
Only shown in this graph, those with at least three publications in the top 120 (2001-2014).

# YOUTH HEALTH: YOUNG RESEARCHER EXPLORES “BIGGER PICTURE”



*Schreier explored how experiences in childhood and adolescence come to influence later-life health.*

**When Hannah Schreier came to Canada from Munich, Germany, on a one-year high school exchange, she had little idea she'd still be on this continent 15 years later, a recognized researcher in health psychology with her own lab at just 30 years old.**

Schreier came to Winnipeg in 2001 on a Grade 11 exchange program, staying on for Grade 12. Then, excited by the prospect of living abroad “a bit longer” and exploring other parts of Canada, she decided to study psychology at McGill University – where she earned the Bertha Lapitsky Award, a Dow-Hickson Scholarship, and the James McGill Award. She then chose the University of British Columbia (UBC) for graduate studies in health psychology, continuing to garner a number of scholarships and awards.

In her research, Schreier likes to take a “bigger picture approach.” Pursuing her Master’s and PhD under Dr. Edith Chen (then Canada Research Chair in Health and Society at UBC, now at Northwestern University), Schreier explored how experiences in childhood and adolescence come to influence later-life health.

“I tried to understand how the social environment gets embedded and comes to influence physiological health outcomes, especially with respect to the influence of, for example, socioeconomic status, and how that shapes longer-term health,” she explains (see *Poor youth, poor health: Unravelling the causes* on page 3 of this issue).

She finds adolescents particularly fascinating. “There are so many changes that individuals go through during adolescence; in some ways I think they’re understudied,” she reflects. “There’s a lot of focus on the very early years, which is very important because of the opportunities for early intervention, but I think there’s a second round of opportunities during adolescence that doesn’t get as much focus as it should.”

In one study while at UBC, Schreier looked at the effects of volunteering on cardiovascular health. She and her colleagues recruited over

100 Grade 10 students, randomly assigning half to volunteer with elementary school children in after-school programs. After four months, students who had volunteered showed more beneficial health outcomes, including lower levels of cholesterol and inflammation. “It was pretty convincing evidence, suggesting that beyond teaching social skills, volunteering might have direct physiological benefits.”

Other publications resulting from her work at UBC examined socioeconomic status in childhood as a predictor of cardiovascular risk in offspring; relationships between family routines and biological profiles among youth with asthma; and how air pollution and stress might interact to affect asthma.

In 2012, Schreier moved from Vancouver to New York to do postdoctoral research in the department of pediatrics at the Icahn School of Medicine at Mount Sinai, supervised by Dr. Rosalind Wright. Her paper on the interaction of mercury and stress during pregnancy was published in *Environmental Health* in March 2015. In August 2015, she began work as an assistant professor in the Department of Biobehavioral Health at the Pennsylvania State University, where she has her own lab and is affiliated with the Network on Child Protection and Well-Being.

Schreier believes that people working in public health, psychology, environmental health, sociology and other fields are increasingly realizing the value – and the need – for interdisciplinary collaboration. “Each one of these groups brings a unique focus that others might not be aware of but which can potentially explain very important aspects of those associations that we’re interested in.” 🦋

**BY EVE KRAKOW**

## POOR YOUTH, POOR HEALTH: UNRAVELLING THE CAUSES

**It is well established that low socioeconomic status (SES) is associated with poorer physical health in young people. Yet while many of the factors involved are well known, few studies have explored how these facets operate through one another or interact to affect health disparities.**

To this end, in 2013, Hannah Schreier, completing a doctorate at the University of British Columbia at the time, and Edith Chen, a professor and researcher now at Northwestern University, reviewed the literature to come up with a more comprehensive model of how SES environments influence youth health. To narrow the scope, they focused specifically on two of the most common health concerns in childhood and adolescence: pediatric asthma and obesity.

There are many pathways through which SES affects child health: the neighbourhood environment, the family environment, and individual characteristics. At each of these levels, there are both physical and social aspects. "There are some associations between these aspects that you might expect, but others that people would not have anticipated," says Schreier of their findings.

In some cases, effects at one level spill over and influence other levels. For example, in lower quality neighbourhoods, where there are fewer parks and public facilities, parents might be less likely to encourage physical activity. Living in a violent neighbourhood has also been linked to worse overall parent mental health and more restrictive parenting, which in turn have been linked to youth asthma and obesity.

In other cases, different levels interact to create unique, synergistic effects. For instance, children exposed to significant social stress are more vulnerable to the negative influence of environmental pollutants and allergens. While the negative effects of these two factors

have been known for some time, "it wasn't obvious that exposure to both at the same time was much, much worse, and that it wasn't just an additive effect," notes Schreier.

The physical and social domains also influence each other: a crowded home can influence family dynamics, creating more conflict and stress, which in turn can affect the ability of families to maintain their home environment. These reciprocal relationships create spiraling sources of exposure, increasing the risk of childhood health problems.

Ross Thompson, a professor of developmental psychology at the University of California, has worked extensively making policy recommendations to try to improve young children's lives. He says that with this paper, Schreier and Chen are encouraging both researchers and policy makers to adopt a more multilevel orientation to their thinking when considering the genesis of health problems.

"A multilevel approach is necessary both for understanding the problem and for think-

ing about what effective interventions are going to look like," says Thompson. From this perspective, interventions focusing on just one factor "may be doomed to failure." Another implication of a multilevel approach is thinking in terms of the potential downstream effects. "In some cases, you can get more significant effects by acting on the family or the neighbourhood than on the child directly."

He also pointed to the importance of timing, both in terms of duration of exposure and critical periods of development. For example, the authors note that SES is particularly influential during early childhood. This suggests that some interventions may be more effective if carried out early in children's lives.

"We need more studies that pull together these different levels of influence," concludes Schreier. "Going even further, we need to get a better sense of the physiological mechanisms that then lead to poorer health outcomes." 🦋

BY EVE KRAKOW

*There are many pathways through which SES affects child health: the neighbourhood environment, the family environment, and individual characteristics.*



# DOES STRESS IN PREGNANCY BOOST ALLERGY RISK?

**Investigators have long been scrambling to figure out why rates of allergic disease are skyrocketing in young people. Now, researchers out of McMaster University have found a new piece to this puzzle: stress during pregnancy.**

**P**etra C. Arck, MD, and colleagues used data on 1,587 children who participated in the Western Australian Pregnancy Cohort (Raine) Study to calculate whether their odds of developing asthma, eczema, and/or allergic rhinitis at ages 6 or 14 were related to their mother's experience of adverse life events during pregnancy. Dr. Arck, now back in Germany, was a senior investigator in the study while holding the position of Canada Research Chair and a professor of neuroimmunology at McMaster.

"Negative life events surveyed in the study were separation or divorce, marital problems, problems with the children, pregnancy prob-

lems, experience of involuntary job loss, partner's involuntary job loss, money problems, a residential move, death of a close relative, and death of a close friend," explains Dr. Arck. "... Among these life events, the more moderately stressful events, such as a residential move, money problems and pregnancy problems, were among the life events most often experienced, whereas more severe life events, such as death of a relative or friend, were rare."

## **NEGATIVE LIFE EVENTS LINKED WITH ASTHMA AND ECZEMA RISK**

It turned out that every negative life event experienced by the mother during the second

half of her pregnancy was associated with more than double the odds that the child would have asthma and eczema at age 14. Interestingly, the link between negative life events and asthma risk was *stronger* if the mother herself had no history of asthma.

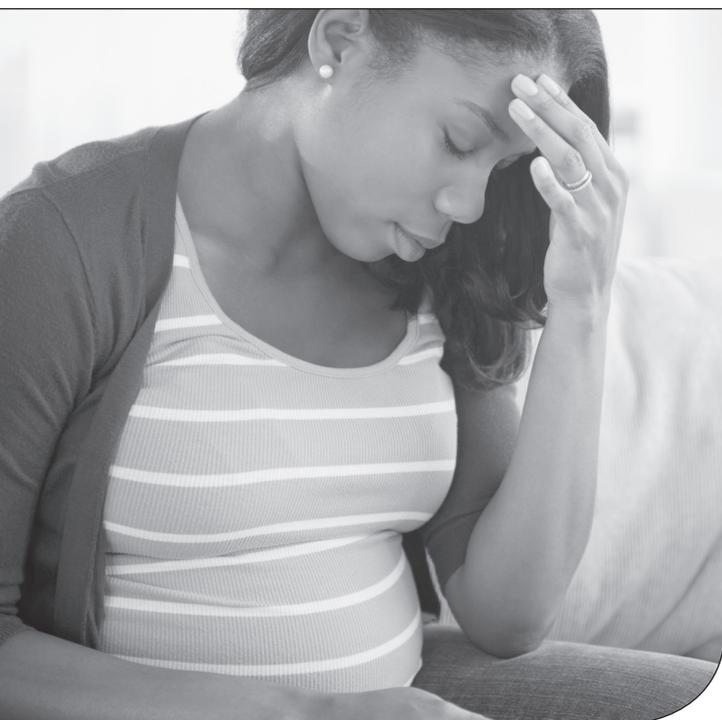
"Immune and lung development occur largely *in utero*, and prenatal environmental stressors may have adverse effects on immune ontogeny and organ development," says Dr. Arck. "This concept is supported by a growing number of studies that newborns to mothers who had experienced high levels of stress during pregnancy demonstrated an altered phenotype of innate and adaptive immune cells in cord blood. Such altered immune status may increase the risk for atopic diseases later in life."

Why was the link weaker among the children of mothers with a history of asthma? The investigators are not sure. "This may be due to the pre-existing high risk due to the high rate of maternal heredity in asthma, which prenatal stress fails to further perpetuate," suggests Dr. Arck.

## **MAKING STRESS REDUCTION A PRIORITY**

Rosalind Wright, MD MPH, of Kravis Children's Hospital, Icahn School of Medicine at Mount Sinai in New York, also studies the effects of stress on disease mechanisms in early life. She says the study findings have implications at both the clinical and policy levels. "A lot of physicians are not counseling pregnant patients around stress and stress reduction and its importance for the child's health as well as the mother's. Physicians talking about this one-on-one during patient encounters will validate for women that this is important because it has long-term implications on the health of their children." From a policy perspective, government programs that help raise families out of poverty can reduce otherwise unavoidable stresses on pregnant women, such as concerns about safety, and access to food, medicine and decent housing. Such measures may help reduce the burden of disease for future generations. 🌱

**BY ALISON PALKHIVALA**



*Interestingly, the link between negative life events and asthma risk was stronger if the mother herself had no history of asthma.*

Ref.: Hartwig IRV, Sly PD, Schmidt LA, van Lieshout RJ, Bienenstock J, Holt PG, Arck PC. Prenatal adverse life events increase the risk for atopic diseases in children, which is enhanced in the absence of a maternal atopic predisposition. *Journal of Allergy and Clinical Immunology* 2014;134(1):160-169.e7. doi:10.1016/j.jaci.2014.01.033.

# PRETERM BIRTH

## IN THE DEVELOPED WORLD

**Preterm birth is the leading cause of death in children under 5 in high-income countries, and the second leading cause worldwide. Yet despite years of research, our knowledge of what causes some 15 million babies to be born at less than 37 weeks' gestation is still quite poor.**

Moreover, the percentage of premature babies is going up, not down. And while attention is usually focused on the developing countries, where rates are highest, numbers in the developed countries are rising too.

"It's a big problem, and a costly one," says Shoo K. Lee, Scientific Director of the Canadian Institute of Human Development, Child and Youth Health. "Understandably, the issues in developing and developed countries are very different."

Lee and his colleagues focused on developed countries: what are the problems here, and what can we do about them? Using data from 39 countries, they sought to estimate how many preterm births could be prevented if current evidence-based interventions were widely implemented. The goal was to establish a rate reduction target for Born Too Soon, an initiative of the World Health Organization (WHO).

It was the first multi-country analysis of trends in preterm birth rates and potential prevention through existing interventions. Specifically, the study focused on smoking cessation, use of progesterone, cervical cerclage, reducing non-medically indicated induction and caesareans, and limiting multiple embryo transfers.

The results were both disappointing and shocking: within the two-year target, if all the known interventions were put into place, researchers projected a mere 5% reduction in preterm births.

The impact is potentially larger in some developed countries than others, however. For instance, in the United States, which has one of the highest preterm birth rates among de-



*"Known causes account for only about 30% of preterm births."*

veloped countries (12%), the primary drivers for rising rates are increasing maternal age, assisted reproductive techniques, non-medically indicated induction and caesarians. In the last few years, a reduction in non-medically indicated procedures has helped push the rate down.

Practices surrounding assisted reproductive techniques also vary from country to country. Whereas European countries typically restrict the transfer of more than one embryo, this practice is allowed in the U.S. and Canada. Implanting multiple embryos increases the chance of twins and triplets, which in turn increases the risk of the babies being born early.

"Reducing rates of preterm birth is perhaps the most serious perinatal challenge facing industrialized countries," notes K. S. Joseph, from the University of British Columbia and the Children's and Women's Hospital and Health Centre in British Columbia. "This review shows just how difficult the challenge is."

Canada's preterm birth rate is in the middle range (7.8%), but still higher than countries such as Finland (5.5%). On the positive side, Joseph points out that sometimes lives are saved precisely because we intervene. "In Canada, we monitor pregnancies very carefully. If the obstetrician sees the baby is having problems, they will deliver early. A decision is made that the baby will do better outside than inside the womb."

However, both Lee and Joseph say that decades of research on preterm births have only made a small dent in the problem so far. "Known causes account for only about 30% of preterm births," Lee admits. "For the other 70%, we have no idea what causes them. We need to put a lot more effort into trying to understand them and figuring out how to address this issue." 🦋

**BY EVE KRAKOW**

# NUTRITION STRATEGIES FOR THE WORLD'S POOREST

**Stunting, where a child's growth and development are compromised, affects some 161 million children worldwide and can have lasting effects on their physical health, learning capacity, and work productivity as adults. Undernutrition underlies 45% of deaths in children under 5 – about 3 million each year.**

**A**s part of a series in *The Lancet*, researchers looked at what can be done, and at what cost. The work updates the journal's 2008 landmark series on the importance of maternal and child nutrition for survival.

"We underscore the value of investing in nutrition-specific interventions that are not only important for survival but also have

developmental benefits," explains Zulfiqar Bhutta, Co-Director and Chair in Global Child Health and Policy at the Centre for Global Child Health at the Hospital for Sick Children in Toronto. He and fellow researchers reviewed a number of evidence-based interventions aimed at women of reproductive age, pregnant women, infants and children. And they looked at delivery platforms: how to best promote behaviour change, access and uptake of these interventions.

Their analysis suggests that 15% of these children – one million lives – can be saved if populations in the 34 focus countries can access 10 interventions at 90% coverage. They showed that investments in the health and nutrition of mothers could have significant benefits for the growing fetus and young infants. Management of severe and acute malnutrition, preventive zinc supplementation in young children, and promotion of breastfeeding showed particular potential.

## INTERVENING EARLY

Early intervention is key – even before pregnancy. "We know that one fifth of all stunting is attributable to fetal malnutrition and being small at birth," says Bhutta. "Some of that is related to nutrition in pregnancy, but some is related to nutrition pre-pregnancy. So you need to go back and have a strategy for interventions that can have intergenerational benefits."

Roughly 10 million girls under 18 are married each year; interventions among adolescents, therefore, to improve nutrition and family planning, to delay the age of the first pregnancy or increase the spacing between pregnancies, might help reduce small-for-gestational-age births in some populations.

The study also notes the importance of nutrition-sensitive interventions – things that are not necessarily in the health sector but that influence nutrition in a tangible way. This includes investments in education, girls' empowerment, agriculture, and water sanitation and hygiene.

## IMPLEMENTATION STRATEGIES

Promising delivery strategies include the use of community events or child health days to scale up coverage in the short term. Such community-based platforms might serve to connect with populations not currently being reached and provide commodities as needed.

Stanley Zlotkin, Chief of the Centre for Global Child Health, says finding the best implementation strategies is precisely the next challenge. He's currently working with four of Canada's largest NGOs to provide a combined evaluation of their projects. "They're doing all the right things in terms of evidence-based interventions," he says. "But we really haven't figured out all of the secrets to implementation." For example, what's the best way to get more women to breastfeed? Instead of seeing efforts invested in 20 different directions, he'd love to have evidence allowing them to concentrate on the few most effective strategies. "We know what to do; the next step is to figure out how to do it efficiently and well." 🦋

BY EVE KRAKOW



*Early intervention is key – even before pregnancy.*

Ref.: Bhutta ZA, Das JK, Rizvi A, Gaffey MF, Walker N, Horton S, Webb P, Lartey A, Black RE, The Lancet Nutrition Interventions Review Group, Maternal Child Nutrition Study Group. Evidence-based interventions for improvement of maternal and child nutrition: What can be done and at what cost? *The Lancet* 2013;382(9890):452-477. doi:10.1016/s0140-6736(13)60996-4.

# IDENTIFYING THE REAL BENEFITS OF BREASTFEEDING

**Breastfeeding is good for mother and baby, but it is not likely to help curb the obesity epidemic, according to unique research coming out of the research team of Michael S. Kramer, MD, at the Montreal Children's Hospital.**

**D**r. Kramer and his collaborators designed and implemented the Promotion of Breastfeeding Intervention Trial (PROBIT). This is the first time that potential long-term benefits of breastfeeding are being assessed in a randomized trial. The data generated have been considered by Health Canada in their development of breastfeeding guidelines, says Jennifer McCrea, Nutrition Advisor at the Office of Nutrition Policy and Promotion.

For PROBIT, more than 17,000 children born in 31 maternity hospitals in Belarus and their affiliated outpatient clinics were randomly assigned to receive either a breastfeeding promotion intervention or to continue their usual practices. The breastfeeding promotion intervention was based on the Baby-Friendly Hospital Initiative developed by the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) and was shown to be highly effective at encouraging both longer durations of breastfeeding and more exclusive breastfeeding during the first year of life in those infant randomized to the intervention group. More than 14,000 continue to be followed up regularly to help determine which health and development outcomes are affected by the breastfeeding intervention.

## NOT A SOLUTION TO OBESITY

A follow-up of the children at 11.5 years of age to assess effects on obesity was disappointing. It appears that encouraging breastfeeding will not help curb the obesity epidemic. These results "disagree with a large number of mostly smaller observations studies that were subject to confounding elements like differences in lifestyle and home environment," says Dr. Kramer. "Those differences are virtually impossible to control for. They include things like TV watching, physical activity level



of the family, and diet over the long term." The randomized trial evenly distributes those confounders and prevents experts from barking up the wrong tree by trying to prevent obesity with breastfeeding, which is not likely to be effective, instead of developing more promising prevention or treatment strategies.

For instance, Health Canada has recently updated its Nutrition for Healthy Term Infants guidelines, which include such important recommendations as promoting infant-led breastfeeding, respecting babies' hunger and satiety cues, and encouraging self-feeding as infants grow into toddlers. "The one thing that remains constant with age is that children should always be in charge of the amount that they eat at any eating occasion and whether they choose to eat at all," says McCrea. "The parent is responsible for providing nutritious food."

## MANY BENEFITS, NO DRAWBACKS

It is important to recognize that while this particular study did not demonstrate a benefit of promoting breastfeeding with regards to obesity, PROBIT has shown many other benefits. These include reduced rates of eczema and

*It appears that encouraging breastfeeding will not help curb the obesity epidemic.*

diarrhea in the first year of life, improved cognitive functioning at age 6.5 years, and improved eating attitudes at age 11. Observational studies have shown that breastfeeding also helps lower the risk that babies will develop ear infections and respiratory tract infections or succumb to sudden infant death syndrome (SIDS). Mothers who breastfeed longer appear to lose their baby weight more quickly and have a delayed return of their menses, which can be important for family planning in the developing world. Importantly, there are no demonstrated adverse health effects of breastfeeding, either for the mother or her child. 🐾

**BY ALISON PALKHIVALA**

Ref.: Martin RM, Patel R, Kramer MS, Guthrie L, Vilchuck K, Bogdanovich N, Sergeichick N, Gusina N, Foo Y, Palmer T, Rifas-Shiman SL, Gillman MW, Smith GD, Oken E. Effects of promoting longer-term and exclusive breastfeeding on adiposity and insulin-like growth factor-I at age 11.5 years: A randomized trial. *JAMA-Journal of the American Medical Association* 2013;309(10):1005-1013. doi:10.1001/jama.2013.167.

# SEXUAL ABUSE AND THE DEVELOPING BRAIN

**Researchers have discovered that sexual abuse early in childhood may affect the very architecture of the developing brain.**

People who experience adversity early in life show a much greater risk of developing a wide range of psychiatric disorders and medical conditions later in life. One common consequence of childhood sexual abuse, for example, is the development of sexual dysfunction. Yet the precise mechanism behind this association is poorly understood.

A group of researchers now believe that when young children are exposed to abuse, their brain adapts to prevent them from fully processing the experience, to shield the child. "But because this happens during a critical development period, at a time when the brain is still forming its connections, the individual does not develop their neural network normally," explains Jens C. Pruessner, a professor in the department of psychiatry at McGill University, and a researcher at the Douglas Mental Health University Institute.

Pruessner and fellow researchers sought to determine whether different forms of childhood abuse were linked to changes in associated areas of the brain. Using magnetic resonance imaging (MRI), they measured the cortical thickness of various regions of the brain in 50 adult women.

They found that exposure to childhood sexual abuse (as reported by study participants) was directly associated with pronounced cortical thinning in the somatosensory field related to the genitals, while emotional abuse was associated with thinning in the regions related to self-awareness and self-evaluation.

"What was striking was that the type of abuse was highly specific to the type of change observed," says Pruessner. "This points to the idea that the brain specifically reacted to the abuse by shielding and protecting itself in the area affected, while leaving other areas intact."

Yet while this adaptation protects the child at the time of the adversity, the authors suggest this lack of development of the genital

sensory representation field may lead to impaired sexual perception later in life, which may explain the frequent clinical reports of sexual dysfunction.

Jean-Yves Frappier, head of the social pediatric division at CHU Sainte-Justine in Montreal, says this study fits into a growing body of research on brain plasticity. "There's a lot of research on the long-term impact of early childhood abuse and adverse events, and how that impact is not only a question of behaviour but is mediated by changes in the brain, and even possibly changes in the expression of genes."

To some degree, Frappier says, these findings do not affect prevention and intervention

strategies: any child abuse should be prevented and acted on immediately, and interventions for resulting disorders in adulthood focus on treating the behaviours.

Eventually, however, there may be ways to treat certain problems medically, if we know the biological or "chemical" cause in the brain and we can target the physiology of the brain. He points to current trials with medications targeting specific genes expression. "If we can say that this part of the brain or this mediator is damaged, is there anything we can do to treat, change or reverse it? One day, we may be able to find treatment that will target these specific changes."

"This is very interesting research," he concludes, "because we are now discovering that adverse events leading to many diseases and disorders seem to have a physiological basis in the brain." 🦋

BY EVE KRAKOW

*Any child abuse should be prevented and acted on immediately.*



# SUPPORTING A LIFETIME OF GOOD COGNITIVE HEALTH

**Use it or lose it. It's a common mantra these days and a driving force behind a trend among seniors to remain physically and intellectually active. But new research suggests that maintaining good cognitive health in old age is not just a matter of picking up a crossword puzzle habit on retirement day. It's a lifelong process, according to research coming out of the laboratory of Sherif Karama, MD, PhD, of the McConnell Brain Imaging Center at McGill University.**

**D**r. Karama and colleagues analyzed data on 588 individuals who formed part of the 1936 Lothian Birth Cohort. Their IQs were measured when they were 11 years old and again when they were 70. When they were around 73, these subjects also underwent magnetic resonance imaging (MRI) to determine the thickness of their cortex at more than 80,000 sampling points.

## LINK BEGINS IN CHILDHOOD

Previous studies have linked greater cortical thickness in old age with preserved cognitive function. This association was confirmed in Dr. Karama's research, but his findings added a new dimension. It turns out that IQ at age 11 accounted for more than two-thirds of the association between IQ at age 70 and cortical thickness at age 73.

"We have seen an association between the thickness of the cortex and preservation of cognitive ability," says Dr. Karama, "but this does not start in old age. It's something that appears to be present all your life." In other words, brain health starts young. How young remains unclear. It may even begin *in utero*.

## MANY QUESTIONS REMAIN

Is the association largely genetic or environmental? That is difficult to tease apart because the two interact. Studies "suggest that roughly 60% of differences in cognitive ability in childhood are accounted for by environmental factors and 40% by genetic factors,"



*Brain health starts young. How young remains unclear. It may even begin in utero.*

says Dr. Karama. "As children age, the heritability of cognitive ability differences appears to increase. That appears to be in part due to the fact that more gifted individuals will tend to seek more stimulating environments. This could, in turn, positively affect cognitive abilities. Such an 'amplification' effect for the more gifted could potentially bias estimates of heritability."

What does this all mean? When studies show a correlation between the brain and cognitive function in older age, it can be tempting to assume that one causes the other, but that still remains to be confirmed. The evidence from Dr. Karama's research suggesting that the link is established much earlier than thought could have implications for identifying and remedying poor cognitive function in childhood, says Jean Séguin, PhD, an expert in

childhood psychosocial development at the University of Montreal. His group's research, as well as that of others, suggests that children who are socioeconomically disadvantaged benefit the most from stimulating environments such as quality daycares. But this research has also shown that those children who need such stimulating environments the most are also among the least likely to receive it. "This does not seem to be a matter of income," he says. Instead it could be because "mothers with less education have different childrearing beliefs and values or a harder time getting the health care services they need. Educated mothers know how to work the system." Public policy must address this discrepancy as it may have implications across the life span. 🦋

**BY ALISON PALKHIVALA**

Ref.: Karama S, Bastin ME, Murray C, Royle NA, Penke L, Munoz Maniega S, Gow AJ, Corley J, Hernandez MV, Lewis JD, Rousseau ME, Lepage C, Fonov V, Collins DL, Booth T, Rioux P, Sherif T, Adalat R, Starr JM, Evans AC, Wardlaw JM, Deary IJ. Childhood cognitive ability accounts for associations between cognitive ability and brain cortical thickness in old age. *Molecular Psychiatry* 2014;19(5):555-559. doi:10.1038/mp.2013.64.

# EPIGENETICS

## AND THE UNDERPINNINGS OF VULNERABILITY

The study of epigenetics, or changes to gene expression that can be influenced by the environment, has turned the nature vs. nurture debate on its head. Now there's yet another twist to the tale, according to new research coming out of the laboratory of Dr. Michael Kobor, PhD, from the Child and Family Research Institute and the University of British Columbia, and conducted in close collaboration with Dr. Joanna Holbrook of the Singapore Institute for Clinical Sciences and Dr. Michael Meaney of McGill University. It turns out that some people's genomes are more susceptible to epigenetic changes than others. This is the kind of finding that can help explain why only some but not all long-term smokers develop lung cancer or why some children fare better than others in the face of early life deprivation or abuse.



*We are all born with genomes that make us more or less susceptible to environmental stressors.*

Using samples taken from umbilical cords, the investigators conducted genetic and epigenetic testing on 237 newborns from the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) birth cohort study. They identified 1,423 regions in the genome where the level of an epigenetic modification (known as DNA methylation) was highly variable across individuals. They calculated that approximately 25% of this variability was due to genetic make-up while 75% was due to the interaction between genetic sequence and the environment *in utero*. These environmental influencers included the mother's smoking habits, depression and body mass index (BMI) as well as the baby's birth weight, gestational age and birth order.

### VARIATIONS IN VULNERABILITY

"The broad idea," says Marco Battaglia, MD, a psychiatrist who specializes in developmental psychobiology at Laval University in

Quebec City, "is that we have a kind of blueprint in our DNA, and there is some variation in it. On top of that, epigenetics can vary the expression of the gene. But more complicated is the fact that you have a genetic influence on the propensity to be liable to epigenetic programming".

The complex relationship between genes, epigenetics and environment helps explain why certain difficult early life experiences have been shown to be detrimental in some cases but not others. For instance, initially no link between epigenetic changes and maternal depression could be found. But an analysis of subgroups revealed that only people with specific genetic sequences are vulnerable to epigenetic changes from maternal depression. In other words, we are all born with genomes that make us more or less susceptible to environmental stressors, such as maternal depression, that may produce epigenetic changes.

### IDENTIFYING VULNERABLE POPULATIONS

"We will perhaps better understand vulnerability and resilience in certain environments when we put together the genetics, epigenetics, and the environment," says Dr. Kobor. "This will allow us to stratify the population and focus on children who are really vulnerable."

This study lays the foundation for measuring genes and epigenetics that are relevant to identifying vulnerable individuals, says Dr. Battaglia. The remaining challenge is to develop operational definitions of environmental factors to allow for the identification, quantification and differentiation of multiple, often interlinked, environmental factors that are likely to be most detrimental in particular populations and which factors should be targeted most heavily in prevention and intervention programs. 🦋

BY ALISON PALKHIVALA

Ref.: Teh AL, Pan H, Chen L, Ong ML, Dogra S, Wong J, MacIsaac JL, Mah SM, McEwen LM, Saw SM, Godfrey KM, Chong YS, Kwek K, Kwoh CK, Soh SE, Chong MFF, Barton S, Karnani N, Cheong CY, Buschdorf JP, Stunkel W, Kobor MS, Meaney MJ, Gluckman PD, Holbrook JD. The effect of genotype and in utero environment on interindividual variation in neonate DNA methylomes. *Genome Research* 2014;24(7):1064-1074. doi:10.1101/gr.171439.113.

# THE INHERITABILITY OF PTSD: IDENTIFYING THE VULNERABLE

**Suffering from post-traumatic stress disorder (PTSD) can be a challenge to raising emotionally-healthy children. Indeed, research has shown that children of parents with PTSD are themselves more susceptible to the condition. Now, the laboratory of Michael Meaney, PhD, at McGill University is starting to explain why.**

Dr. Meaney specializes in the study of epigenetics, or changes in genetic expression that occur as a result of environmental influence and which may be inherited by the next generation. He has joined forces with Dr. Rachel Yehuda, from the Icahn School of Medicine at Mount Sinai, who has shown that children of Holocaust survivors are more vulnerable to PTSD and are more likely to have an endocrine “signature” characterized by low production of cortisol. “Cortisol can be protective against PTSD,” says Dr. Meaney, “particularly in [those] who live in stressful circumstances.”

## COMBINING EXPERTISE

Could epigenetics play a role in this intergenerational association of parental PTSD with PTSD-related vulnerability in offspring? To find out, Dr. Meaney and colleagues identified 80 adults with at least one parent who was a Holocaust survivor and 15 adults of similar background whose parents were not in the Holocaust and did not have PTSD. They compared these two groups with respect to multiple psychological and biological factors.

Participants whose fathers, but not mothers, had PTSD (whether or not they were Holocaust survivors) had evidence of an epigenetic change consisting of higher methylation on the NR3C1 gene, which encodes for the glucocorticoid receptor. In contrast, those in whom both parents had PTSD had reduced methylation of this same gene. The investigators also demonstrated that increased methylation silences the activity of the gene and is associated with reduced cortisol suppression during a cortisol suppression test.

Similarly, the presence of symptoms of psychological distress in the subjects differed

depending on whether their mother or father had PTSD. Those whose mothers only had PTSD were most likely to suffer from psychological scars, low perceived emotional health, depressive symptoms and anxiety. Those whose fathers only had PTSD also had some signs of psychological scars and anxiety, but they were more likely to suffer from problems associated with childhood trauma, such as sensitivity to stress and varieties of insecure attachment. If both parents had PTSD, offspring suffered the whole gamut of symptoms, but remarkably, their NR3C1 gene methylation was similar to those who had parents without PTSD.

## PUTTING IT TOGETHER

Why the gender of the parent with PTSD is so significant remains unclear, but it is increasingly certain that children of people with PTSD are vulnerable at the level of biology and symptomatology. This work raises the hope that one day laboratory testing can be

used to identify the most vulnerable people among at-risk populations using such biological markers as gene methylation much in the way blood tests are used today to help predict heart attack risk.

John O’Neil, MD, an expert in post-traumatic and dissociative disorders at St Mary’s Hospital Center calls this “a marvelous example of where research needs to go... If you could match epigenetic changes to the resultant hormonal differences in children, then you would presumably be able to identify those that would be more susceptible to developing subsequent PTSD. Identifying whether these epigenetic changes are transmitted in the germline would be of enormous scientific interest, but in either case, since epigenetic changes are environmentally induced, in whichever generation, psychosocial interventions would remain crucial in treatment.”

BY ALISON PALKHIVALA

*Children of people with PTSD are vulnerable at the level of biology and symptomatology.*



# KEEPING MOTHERS HEALTHY: HOW ARE WE DOING?

**Optimizing women's health during pregnancy and birth so they can take care of their children is a priority for the United Nations. That's why they made a 75% reduction in maternal mortality rate (MMR), one of eight Millennium Development Goals toward ending poverty worldwide.**

So, how are we doing? That's what Nicholas J. Kassebaum, MD, from the Institute for Health Metrics and Evaluation (IHME) at the University of Washington is monitoring, in collaboration with experts worldwide, including those from the Public Health Agency of Canada.

Results published in September 2014 in *The Lancet* reveal a mixed picture. Some countries, like China, are doing tremendously well, says Dr. Kassebaum. They are managing to lower MMR rates with strategies that are known to work, including having women give birth in

specially-designated facilities or at least with a skilled attendant present, even for straightforward deliveries. Some promising interventions have failed to show strong benefits, but Dr. Kassebaum warns against abandoning them too soon. For instance, the benefits of emergency obstetric care (EmOC) may be difficult to demonstrate at the population level when its quality and coverage remains inconsistent from region to region, but that means it should be improved, not abandoned. Similarly, it is logical to assume that "getting women on the radar of health care is a good thing," even

if hard data on the mortality benefits of routine antenatal care are lacking. Even simple interventions are beneficial, such as teaching women to recognize when they may be having pregnancy or labour problems so that they can seek out help in a timely manner.

Some regions, particularly Central and Western Africa and regions around the Horn of Africa, are still struggling. They must concentrate on developing integrated delivery and emergency services so that women who are having complications get the life-saving care they need, says Dr. Kassebaum.

An interactive visual representation of the world's progress in meeting the Millennium Development Goals can be found at [vizhub.healthdata.org/mdg](http://vizhub.healthdata.org/mdg). 📊

BY ALISON PALKHIVALA

Ref.: Kassebaum NJ, Bertozzi-Villa A, Coggeshall MS, et al. Global, regional, and national levels and causes of maternal mortality during 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. *The Lancet* 2014;384(9947):980-1004. doi:10.1016/s0140-6736(14)60696-6.



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