Evidence and implications for research and action – a summary

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The international workshop held in Montreal on 6–9 June 2004, and organized by the WHO Collaborating Centre TRANSNUT of the Department of Nutrition, Université de Montréal, addressed the influences of early nutrition on chronic diseases later in life. This summary paper contains highlights of the speakers' presentations and background data from the literature. It also integrates the questions and concerns raised by the workshop participants regarding future research and intervention programmes.

Increased risk of chronic disease: prenatal and postnatal environments

Fetal programming is one of the mechanisms through which poor early nutrition and later risk of chronic disease may be connected. Programming by early nutrition represents a predictive adaptation to a likely unfavourable postnatal nutritional environment. The association of suboptimal early growth and nutrition with increased chronic disease risk later in life is now explained as a mismatch between the early nutritional environment, particularly the intrauterine environment, and that of the outside world (Gluckman *et al.*, 2005). Going from a constrained nutritional environment *in utero* and perhaps also in early infancy to abundant nutrition after 2 years of age represents this mismatch. The 'survival' or 'thrifty phenotype' of Hales & Barker (1992) is not only

smallness at birth (low birthweight and ponderal index), but also a higher percentage of body fat. The 'cost' of this survival-adapted phenotype is a greater risk of chronic disease in later life if the environment is conducive to overeating and a sedentary lifestyle (Gluckman & Hanson, 2004).

Rapid child growth may add to the risk associated with poor growth and nutrition *in utero* and in early infancy

There is evidence of sensitivity to nutritional programming in the postnatal period and not only during fetal life. Infant growth patterns are not independent of fetal growth and there may be a synergistic effect of low birthweight and accelerated postnatal growth (Cole, 2004). Some researchers even contend that postnatal growth, particularly if it is rapid, is the main factor associated with later risk of chronic disease, whereas prenatal growth is merely a determinant of postnatal growth (Lucas *et al.*, 1999). It is therefore important to consider both stages jointly rather than in isolation. In addition, birthweight is only a proxy for fetal growth, and there are high long-term risks at both ends of the birthweight spectrum (Gillman, 2002a). At one extreme is restricted fetal growth and its potentially adverse impact on chronic disease risk, particularly for individuals exposed to other risk factors during their lifecourse; at the other is high birthweights associated with an increased risk of gestational diabetes, the rate of which is increasing as young women become more obese, resulting in enhanced risk of obesity.

There is strong evidence that growth during childhood modifies the risk established *in utero* (and early infancy), in light of cohort studies in industrialized

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and developing countries, although at this time only four large birth cohorts exist in developing countries, in Asia and in Latin America, but none in Africa. Based on large cohort studies in Finland (Eriksson, 2005) and on data from the few cohorts in developing countries (Stein *et al.*, 2005), it appears that accelerated weight gain past early childhood and at least up to the age of 12 in individuals born small is linked with a higher risk of diabetes, hypertension and coronary heart disease (CHD). However, early and late postnatal growth need to be delineated. In lower birthweight newborns, catch-up during infancy may be beneficial, as the highest risk is observed in those remaining small at 1 or 2 years. While rapid or accelerated or catch-up growth may be associated with elevated chronic disease risk in later life, there seems to be a window of 'growth restoration' (Solomons, 2005) with health benefit rather than risk, in the first couple of years.

Coronary heart disease, diabetes and even obesity are associated with different growth trajectories (Barker, 2003). Furthermore, the impact of accelerated growth may not be the same in developing countries and in industrialized countries, as fetal undernutrition is much more widespread in the former than in the latter. This is one reason for the need for more data on lifetime height and weight trajectories in different contexts. There is also a need to distinguish between 'accelerated growth' and 'catch-up growth', to define whether it is growth in weight or height, and to refer to specific periods in childhood. Existent data suggest that rapid weight gain in childhood is associated with increased risk of obesity and chronic diseases; this may not be the case for accelerated linear growth.

Postnatal growth patterns may have closer links with later obesity than size at birth, either independent of size at birth or in interaction with it. Restricted fetal growth appears to be associated with greater abdominal fat in later life, whereas augmented birth weight predicts higher body mass, but more lean body mass rather than more body fat. Many studies suggest that there is better tracking of high body mass index (BMI) into adulthood for school-age than preschool-age children (Guo *et al.*, 1994; Wang *et al.*, 2000). In Guatemala, Brazil and

Jamaica (Schroeder *et al.*, 1999; Hoffman *et al.*, 2000; Walker *et al.*, 2002; Sawaya *et al.*, 2005), stunting in childhood was found to be independently associated with a higher risk of central obesity. Greater susceptibility to the effects of high-fat diets has been proposed as an explanation for the link between childhood stunting and adult obesity (Sawaya *et al.*, 2005), because of impaired fat oxidation.

Breastfeeding may be protective against obesity and associated risks

There are epidemiological concerns with studies on the relationship between breastfeeding and subsequent obesity, notably residual confounding effects of socio-economic factors (Hediger *et al.*, 2001). Nonetheless, evidence for a protective role of breastfeeding against obesity is growing, with up to 30% risk reduction (Gillman, 2002a). One of the plausible mechanisms is that breastfeeding may promote better self-regulation of food intake than artificial feeding (Fisher *et al.*, 2000; Poothullil, 2001). Children normally adjust their caloric intake, except when there is feeding restraint (Faith & Kerns, 2005). Indeed, Fisher *et al.* (2000) reported that highly controlling feeding strategies on the part of the parents are positively associated with adiposity and the child eating highly palatable snack foods in the absence of hunger. Breastfeeding through the first year may also establish a greater degree of maternal responsiveness to infant cues and foster a shared mother-child responsibility in the regulation of intake. Breast-fed infants are exposed to flavours and odours of the maternal diet, which facilitates the transition to and an acceptance of a wide range of solid foods. Interestingly, breastfeeding has been shown to be an independent predictor of fruit and vegetable consumption by preschool children (Cooke *et al.*, 2003).

The association between breastfeeding and cardiovascular disease risk markers requires further study. A recent systematic review and meta-analysis of data on the association of breastfeeding with blood pressure in later life (Owen *et al.*, 2003) concluded that it had only a modest preventive role that was likely of limited public health importance (-1.1 mmHg systolic blood pressure). However, the review did suggest that

breastfeeding may be associated with long-term lower total cholesterol levels.

The long-term impact of the early diet, that of mothers as well as that of infants, is still not well documented in human studies. For instance, very long chain polyunsaturated fatty acids have been shown to be important for fetal and infant growth, as well as central nervous system development. Much inconsistency still exists, however, on this topic. In addition to early programming, social patterning of eating habits may play a role in chronic disease risks (Faith & Kerns, 2005). This may partially explain why parental obesity is the strongest predictor of child overweight. Mother-imposed food restriction in childhood appears to have the same predisposing effect to dys-regulated eating and excess body fat accumulation as self-imposed restriction in adulthood (Fisher & Birch, 1999; Birch *et al.*, 2003; Faith & Kerns, 2005). One unanswered question is 'To what extent maternal nutrition acts biologically or behaviourally, prenatally or postnatally' (Law, 2001). The genetic influences on dietary behaviours in humans remain an interesting challenge for research (Faith & Keller, 2004).

Early influences in populations undergoing nutrition transition are a serious concern

Nutrition transition refers to profound changes in lifestyles and eating patterns that are fuelled by urbanization, globalization and growing incomes. These changes are characterized by increasingly sedentary lifestyle and atherogenic diets (Popkin, 1998). The effects of nutrition transition are also aggravated by a legacy of low birthweights from the previous generation (Haddad, 2003). Nutrition transition is contributing to the growing rate of obesity, diabetes and CVD in developing countries, in groups migrating to industrialized countries and among aboriginal populations. However, the nutrition transition process may not be identical in all settings and age groups. The speed of nutrition transition is critical because the change in the postnatal environment is faster than that of the prenatal environment (Barker, 1998; Gluckman *et al.*, 2005). The prenatal environment is determined by mother's size, body composition and

metabolism, which is partly determined in turn by her own growth *in utero* and during infancy and childhood. In the nutrition transition context, small mothers have small babies because of maternal size constraints, and then the children grow rapidly owing to more favourable factors in the postnatal environment.

Both obesity and undernutrition coexist in nutrition transition areas, which imposes a double nutritional burden on societies and health systems. The coexistence of maternal overweight and child stunting in the same household (Garrett & Ruel, 2005) is typical of rapid nutrition transition, and it is reportedly more widespread in Latin America than in Africa and Asia. It illustrates the differential rate of change of the prenatal and postnatal environment. Household food insecurity may be involved, with poor diet quality resulting in malnutrition in children while in adults, nutrient-poor but energy-dense diets predispose to obesity.

It was observed in Brazil (Sawaya *et al.*, 2005) that child stunting, which is an indicator of chronic malnutrition, was associated with a higher risk of obesity. This suggests that fetal and early childhood malnutrition may further exacerbate the chronic disease risk associated with accelerated growth owing to ample food supplies and better health care.

Animal models of early programming by nutrition during gestation and suckling

Rat models examining fetal and postnatal programming by nutrition have revealed that it is possible to induce hypertension, diabetes and metabolic syndrome, but not coronary disease (Langley-Evans *et al.*, 2005). Interactions between prenatal and postnatal nutrition are illustrated, among others, by the observation that rat offspring from protein-restricted dams exhibit catch-up growth when suckled by a normally fed dam, but die younger compared to the offspring of normal dams which are suckled by protein-restricted dams (Hales & Ozanne, 2003). Hyperphagia was observed in adult offspring which had been exposed to maternal undernutrition (Vickers *et al.*, 2000). In the rats from underfed mothers, postnatal

hypercaloric nutrition also amplified the metabolic abnormalities induced by fetal undernutrition. It appears that increased appetite and hyperphagia may also be programmed during lactation, as observed in weaned rats that were suckled by protein-restricted dams. Rats from protein-depleted mothers also put on more abdominal fat than normal controls when weaned on a high fat diet. Protein restriction *in utero* appears to disrupt regulation of energy intake in rats.

Vickers *et al.* (2003) observed that the rat offspring of underfed dams were significantly less active than those of well fed mothers at all ages studied, independently of postnatal nutrition. Furthermore, their sedentary behaviour was exacerbated by postnatal hypercaloric nutrition. These findings suggest that the well known association between obesity, the metabolic syndrome, sedentary behaviour and overeating may have a common determinant in prenatal life, and lifestyle choices may also have a perinatal component. The co-occurrence of undernutrition prenatally and of excess nutrition postnatally seems to be the most powerful predictor of obesity, at least in animal models.

Research needs

Because of the knowledge gaps in interactions between postnatal and prenatal growth and nutrition, it was felt that specific recommendations based on early programming of chronic diseases would be premature. The urgent need for additional research in this area was reiterated throughout the workshop, particularly for longitudinal studies in populations exposed to different maternal, fetal and infant nutrition factors, so that commonalities and differences may be identified and the practical implications highlighted.

As suggested by Gillman (2002b), epidemiological studies of the following types will be particularly valuable: (1) New prospective studies of pregnant women with follow-up of offspring over time; (2) Follow-up of adult cohorts in whom biological samples and prospectively collected epidemiological data are already available; and (3) Follow-up into childhood or adulthood via randomized controlled trials conducted during pregnancy.

A priority is to reanalyse existing data from both developed and developing countries to assess the full impact of catch-up growth on health both in the short- and long-term (Victora & Barros, 2001). Usually, rapid weight gain, particularly if the child is born small, is the target of growth monitoring and promotion programmes. In view of the higher chronic disease risk found to be associated with poor early growth, as well as with rapid catch-up growth past infancy, the short- and long-term benefits of catch-up growth in growth-restricted newborns have to be investigated according to the timing and type (weight gain, height gain) of catch-up growth.

High quality dietary intake data are direly needed, in children and women cohorts. Future research may reveal that not only protein and carbohydrate imbalances are involved in early programming of chronic disease risk, but also those of long chain polyunsaturated fatty acids, folate, iron and other micronutrients. Research on nutrient biomarkers is also warranted.

Research in the area of diet transition in developing countries is in its infancy. This type of research is highly relevant considering the rapid changes in the nutritional environment that it entails. Haddad (2003) suggested using existing nationally representative household survey data to chart trends in the availability of 'unhealthy' dietary components, and to spell out the trade-offs in terms of the consumption changes of different dietary components.

Implications for policy and programmes

More studies are indeed required, but action should be taken now, based on the best available evidence.

Addressing nutritional transition now

There is a need to address simultaneously the prevention of obesity and of undernutrition, as they often coexist as a result of rapid nutrition transition. Hardly any programme focuses on both, except perhaps for the diet quality index and food guide pagoda developed in China (Stookey *et al.*, 2000). Convincing decision-makers at the government level in developing countries of the need to address obesity and chronic

diseases is not simple, as they are considered diseases of the rich. It even creates a 'cultural shock' (Solomons, 2005), as policies and programmes have been focusing on food insecurity, undernutrition and micronutrient deficiencies. Governments must feel the pressure. Diabetes may be a key word, as the associated health costs are enormous, and health ministries are well aware of them (James, 2005). Linking diabetes with child obesity and with maternal risk may be a worthy strategy.

Women's empowerment is key

One policy option to attenuate the impacts of dietary transition is to reduce impaired fetal growth, and this is about targeting women as early as possible in their life. For instance, Popkin *et al.* (2001) estimated that in China, approximately one-third of diabetes could be traced to low birthweight and stunting in infancy. Empowerment of women has been propounded (Solomons, 2005), although effecting change at this level is a great challenge. Interventions to improve maternal diets and to promote breastfeeding are relevant everywhere, irrespective of the fact that little is known of the programming effect of specific dietary components and their timing. Interventions to prevent undernutrition and obesity among women of childbearing age is complex but may deliver long-term benefit to their children (and the women themselves).

Toddlers and children: avoidance of accelerated weight gain and prevention of obesity

Low weight or body mass in infancy should remain a concern since it is independently associated with increased chronic disease risk. Adequate growth should be sought in the first 2 years of life, with particular attention to infants born small. During childhood, the avoidance of accelerated weight gain, even among those of normal BMI is the main strategy to reduce the risk of obesity and metabolic syndrome (Eriksson *et al.*, 2003). It is still not known, however, whether it is feasible, appropriate or safe to modulate the early diet according to infant growth phenotype.

Among children, the priority should be to prevent them from becoming obese; food promotion plays an

important role. The most widely advertised foods, particularly in industrialized countries, are sweet breakfast cereals, confectionery, savoury snacks, fast foods and soft drinks (James, 2005). We have to think of means to promote wholesome foods so that they become desirable to children (and adults), and to make them less expensive. Additionally, we should not forget the importance of exercise, which decreases the risk associated with suboptimal early growth and nutrition (Eriksson, 2005). Based on evidence, children born small are a group to target through interventions to prevent obesity. It is likely more cost-effective to focus on children rather than adults for the prevention of obesity, but more research is required to assess the efficacy of such programmes in children. Current nutrition programmes for children in developing countries may need to be adjusted so that they do not contribute to obesity, as observed in Chile (Uauy & Kain, 2002).

We may conclude from the Workshop that postnatal nutrition interacts with prenatal nutrition, but that more research is needed before specific policy changes can be recommended. With further knowledge, it might be possible to identify, via markers of fetal insults, those individuals who need more intensive interventions because of their heightened risk profile. It might also be possible to manipulate maternal nutritional factors during pregnancy and lactation, as well as infant feeding and growth, to proactively minimize the risks associated with early suboptimal nutrition. Efforts at preventing obesity in populations undergoing epidemiological and nutrition transition are of paramount importance. Additionally, improving women's health and nutrition status as early as possible in their life may go a long way towards improving the well-being of the present and subsequent generations. Whether in developing country or in industrialized country children, maximum growth may not be optimal, at least past early infancy, and it should not be the target.

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