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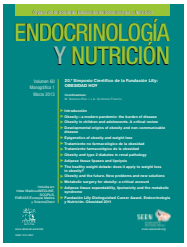

20.º SIMPOSIO CIENTÍFICO OBESIDAD HOY

Developmental origins of obesity and non-communicable disease

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Non-communicable diseases (NCDs) such as cardiovascular disease, diabetes, chronic lung disease, and some forms of cancer are the world's biggest killers. 80% of these deaths occur in low and middle income countries, especially as these countries undergo socio-economic improvement, following reductions in the burden of infectious disease. The problems are exacerbated by more sedentary lifestyle and Western diets high in sugar, salt and fats. Obesity is a major risk factor for such NCDs. WHO predicts an increase of 17% in NCDs over the next decade globally.

Recent data show that risk markers for NCDs become evident early in the process of socio-economic improvement and well below the level of affluence associated with them in developed societies. Worse still, in developing countries many people are suffering from NCDs in their thirties. The financial costs of these diseases are of great concern. Ten times as many people suffer from NCDs as from HIV AIDS, and the likely economic impact of NCDs eclipses global warming, according to the World Economic Forum.

But NCDs are preventable, although such prevention was missing from the Millennium Development Goals. So new initiatives are needed. This was addressed by the UN high level meeting on Prevention and Treatment of NCDs held in September 2011 (www.un.org/en/ga/ncdmeeting2011/). It is becoming increasingly recognised that the current programmes aimed at obesity reduction in adults are not working.[1] In addition, progress in understanding NCD prevention has been slow due to excessive emphasis on fixed genomic variations as determinants of susceptibility. This deterministic approach has compromised progress in understanding of development and inheritance of NCD risk. We now know that fixed genetic variations (for example small mutations, repeat sequences) can account for only 5-10% of such risk at the maximum. Attention now needs to be paid on how risks are established in early life. Prevention necessitates understanding how the developmental environment influences an individual's responses to their later lifestyle, processes which involve non-genomic inheritance, especially epigenetic processes. These affect gene expression and development without altering the genes we inherit from our parents.

New evidence demonstrates opportunities for novel biomarkers of risk to be devised for use in early life. This may pave the way to much more effective, customised interventions to promote health across the lifecourse. For example, we recently showed that measurement of an epigenetic change in perinatal tissues at birth can predict more than 25% of the variation in body fat in children aged 6-9 years.[2] Further, this epigenetic change is related to the mother's diet in pregnancy. In experimental studies such epigenetic changes are mechanistically linked to altered metabolic function and, importantly, can be reversed by developmental interventions.

Specific aspects of the developmental environment, such as the mother's diet or her body composition, stress levels, her level of physical activity, her age and whether this is her first pregnancy have been shown to affect risk factors for later disease in her children. These factors operate in all pregnancies, to a greater or lesser degree. During development, aspects of the external environment are transduced by the mother, during both fetal life and nursing. Signals from the mother to the developing embryo, fetus and infant operate via developmental plasticity to affect the characteristics of the offspring.

Such influences on the offspring appear to have evolved because they confer Darwinian fitness by inducing charac-

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teristics appropriate to the environment in which the mother lives: we termed these predictive adaptive responses (PARs). The characteristics affect particular aspects of lifecourse biology such as metabolic control, allocation of fat, skeletal muscle, cardiomyocyte and nephron numbers and the settings of control systems such as appetite, stress responses, timing of puberty, etc.[3] Together they affect the ways in which the adolescent and adult respond to their environment. Where these responses include appetite and food preference, physical activity propensity, fat deposition, etc, they thus influence the person's risk of later NCD. Because the PARs will be slightly different in each individual, they contribute to the differences in risk of disease between individuals, even if they apparently have very similar lifestyles.

However, developmental changes made on the basis of predictions can turn out to be inappropriate, either because the signals sent by the mother to her offspring are inaccurate, e.g. as a result of placental dysfunction or because she consumes an unbalanced diet, or as a result of her own development and lifecourse, or because the environment has changed from one generation to the next. If this occurs, there is a 'mismatch' between the offspring's characteristics and the environment in which they live.[4] Mismatch thus confers a major risk of NCDs. We now know that the processes of mismatch also operate across the spectrum of environmental signals too, for example an unbalanced maternal diet which is inadequate in a low income setting can be as potentially harmful as the high glycaemic diet of many western societies.

Whereas the initial focus was on children who were born small and who might therefore constitute only a small proportion of the population, it is now clear that the developmental environment impacts on the developmental trajectory of every child. The story does not end at birth: epigenetic development can be influenced by how the child is fed after birth, with infection or allergen exposure and perhaps how the gut is colonised with commensal bacteria. Phenotypic outcomes having long-term consequences involve the interplay between genetic, developmental and environmental influences. It is impossible to pull them apart.

The long-term effects of unbalanced nutrition before and during pregnancy and lactation are very significant, and involve both under- and over-nutrition in many societies. Of particular concern is the rise in obesity and excessive weight gain in pregnancy in many populations. In addition nearly 80m women worldwide suffer from gestational diabetes and this over-nutrition state for the fetus also increase risk of obesity, diabetes and other NCD in the next generation. Thus there are successive cycles of disease risk on a global scale, exacerbated by socio-economic, lifestyle and demographic changes. We need to pay urgent attention to this global epidemic —for economic and political as well as humanitarian reasons.

Conflicts of interest

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