Obesity: Childhood obesity: Time bomb for future burden of chronic liver disease

Please note the following before checking your manuscript

Dear Professor Bugianesi,

Please note:

- Queries may be nested in the addresses section or in the reference list, please look out for these.
- References that could be in any way misread (for example, those that follow numbers or symbols) are usually set in brackets, on the line.
- Please check reference numbering carefully, as they may have been renumbered (for example, to avoid duplications).
- When marking up your corrections, please use the Commenting tools only (do not edit the text directly).
- If your article has Supplementary Information but you have not received the file(s) along with this proof, please let us know as soon as possible.
- We do not usually edit Supplementary Information in house, so should you require changes to your SI, please send a revised file and indicate what changes have been made.

OBESITY

Childhood obesity: time bomb for future burden of chronic liver disease

Milena Marietti and Elisabetta Bugianesi

A recent study reports that being overweight in late adolescence is associated with an increased risk of liver-related morbidity and mortality later in life. These findings give further strength to the concerns for the deleterious effects of childhood obesity on liver health. Early prevention by screening and lifestyle modification should be advised by health policies.

Refers to Hagström, H. *et al.* Overweight in late adolescence predicts development of severe liver disease later in life: a 39 years follow-up study. *J. Hepatol.* **65**, 363–368 (2016)

With over one billion individuals with obesity expected worldwide by 2030, obesity is undoubtedly the most prominent single disease of the 21st century and a gateway for ill health, increasing the risk of a variety of related comorbidities[1]. Concurrent with the obesity epidemic, NAFLD is rapidly becoming the leading cause of chronic hepatitis in the Western world; in NAFLD, the histological features of steatohepatitis and fibrosis are associated with an increased risk of progression to end-stage liver disease (ESLD), hepatocellular carcinoma (HCC) and indication for liver transplantation[2,3]. Over the past few decades, obesity has shifted towards an onset earlier in life with a dramatic rise in occurrence in childhood: from 5.0% in 1960 to 16.9% in 2009–2010 (REF. 4). This finding represents a serious threat to the health state of our children and raises the issue as how this earlier advent of overweight will affect the burden and management of NAFLD later in life. The study by Hagström *et al.*[5] gives a meaningful insight on this issue (BOX 1). The researchers evaluated a general population cohort of 44,248 men aged 18–20 years that attended an outpatient visit for conscription into military service in Sweden between 1969 and 1970 and tested the association of basal BMI on liver-related morbidity and mortality based on hard, statistically significant end points such as the development of ESLD, cirrhosis, or liver-related death (in National Patient and Causes of Death Registries). After a follow-up of almost 38 years, 393 patients developed ESLD, of which 213 died; basal BMI was a strong and independent predictor of ESLD and mortality later in life. Being overweight in late adolescence increased the risk of liver-related outcomes by 64% compared with a low–normal range BMI and each unit increase in BMI increased by 5% the liver-related outcomes[5].

This new study definitively establishes that the obesity-related risk of future severe liver disease starts early in life, though the overall effects can be underestimated as the proportion of overweight and obesity was rather low in this late 1960s cohort compared with now. The study did not take into consideration weight trajectories, but early adulthood weight-gain seems to carry a higher risk of mortality than weight-gain in late adulthood. In a large longitudinal Danish study[6], a gain in BMI between 7 and 13 years of age was positively associated with each clinical and histological stage of adult NAFLD (steatosis, steatohepatitis, fibrosis and cirrhosis) when adjusted for initial as well as attained BMI. Among children with similar attained BMIs at 13 years of age, those who gained in BMI had a 16% increased risk of adult cirrhosis per 1-unit gain in BMI z-score[6]. Thus, a weight gain during school-years is able to induce an increased susceptibility of developing NAFLD later in life.

Why excessive weight gain in childhood seems to influence the entire spectrum of liver damage in NAFLD is not known. Although childhood and adult obesity are correlated, the tracking is generally moderate in magnitude. This finding indicates that other mechanisms are also at play. In the Cardiovascular Risk in Young Finns Study[7], the childhood predictors of adult NAFLD at follow-up of 31 years were childhood demographic and metabolic variables (BMI and insulin levels), but also non-modifiable risk factors, such as male sex, genetic background (that is, *PNPLA3* and *TM6SF2* variants) and low birth weight, the latter probably related to epigenetic regulation in an adverse intrauterine environment. Furthermore, other obesity-associated comorbidities, such as diabetes mellitus, could have a direct role in promoting liver damage.

Box 1 | **Key findings and take-home messages**

- NAFLD has gained clinical recognition as main cause of liver disease in children and adults as a consequence of the pandemic spread of obesity, particularly in children
- Overweight in late adolescence is associated with an increased risk of liver disease due to NAFLD later in life; as a consequence, the threshold of liver-related morbidity and/or mortality is reached at a younger age
- Weight gain during school-years carries a higher risk of NAFLD than weight-gain in late adulthood
- High BMI during childhood has been linked to an increased risk of primary liver cancer in adulthood
- Identification of children at risk of future liver disease because of their childhood BMI is advisable according to current guidelines on NAFLD
- Prevention of excessive weight gain during childhood and lifestyle modification during early adulthood including weight loss should be advised by health policies to reduce the risk of early liver disease

An important piece of information missing in the report by Hagström *et al.*[5] is the link between obesity early in life and the risk of HCC arising decades later, but this association has already been described. A study[8] including schoolchildren in Copenhagen showed that each unit increase in BMI z-score, at every age from 7 through 13 years, increased by 20–30% the risk of liver cancer 30 years later. To put this in perspective, compared with an average height and weight 13-year-old boy, a boy of similar height but who weighed 6 kg more would have a 30% increased risk of liver cancer. Similarly, a US study has shown that a prior history of obesity in early adulthood was more common in HCC cases than in matched controls (no obesity onset in early adulthood)[9]. Obesity in the mid-twenties age bracket hastened by 4 years the occurrence of HCC, whereas obesity in the mid-thirties age bracket was associated with a diagnosis of HCC 5 years earlier.

> “…NAFLD is rapidly becoming the leading cause of chronic hepatitis in the Western world…”

The findings by Hagström *et al.*[5] have both clinical and socioeconomic implications. In this population, ESLD due to severe liver disease occurred ~45 years of age, which is an exceedingly early occurrence as NAFLD progresses slowly and cirrhosis is unusual in young individuals[3]. From the clinical point of view, this finding means that when overweight and obesity are present since adolescence, the threshold of liver-related morbidity and/or mortality due to NAFLD is reached at a fairly young age. Most importantly, NAFLD and its complications are more likely to be anticipated in later life when obesity is present since childhood: in essence, the timeframe for injury to the liver is shifted forward but other factors that might have a role need to be clarified **[Au: addition OK?]**. This aspect will unavoidably lead into a remarkable reduction of life expectancy and a substantial additional societal burden.

How do these findings translate into clinical practice? Importantly, the deleterious effects of obesity on liver health should not be overlooked, particularly during childhood. Children are the most vulnerable population and deserve a careful evaluation according to the European Association for the Study of the Liver, European Association for the Study of Diabetes and European Association for the Study of Obesity joint guidelines on NAFLD[10]. Also, individuals with a long duration of being overweight should be screened for liver disease according to the same guidelines[10] — the earlier the onset of obesity plus the longer the duration, the higher the risk of NAFLD — and they should avoid other risk factors for liver disease, such as occasional alcohol abuse or potentially hepatotoxic drugs. Although waiting for the development of an effective drug therapy of NAFLD, the guidelines[10] include obesity control as a priority to reduce the burden of liver disease in the community. Combined efforts by all health-care providers and societal strategies at the population level to control childhood and early adulthood obesity should be an immediate priority. If we are going to lose the battle of halting ‘obesigenic’ lifestyle, the expected decrease in the liver disease burden achieved with the discovery of effective therapies for viral hepatitis will be rapidly reversed by the epidemic of obesity.

M. Marietti and E. Bugianesi are at the Division of Gastroenterology, Department of Medical Sciences, University of Torino, AOU Citt→ della Salute e della Scienza, Corso Dogliotti 14, 10126 Torino, Italy.

Correspondence to E.B.
elisabetta.bugianesi@unito.it

doi:10.1038/nrgastro.2016.120
Published online DD Mon 2016

1. Kelly, T., Yang, W., Chen, C. S., Reynolds, K. & He, J. Global burden of obesity in 2005 and projections to 2030. *Int. J. Obes.* **32**, 1431–1437 (2008).
2. Yki-Järvinen, H. Non-alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome. *Lancet Diabetes Endocrinol.* **2**, 901–910 (2014).
3. Bhala, N., Jouness, R. I. & Bugianesi, E. Epidemiology and natural history of patients with NAFLD. *Curr. Pharm. Des.* **19**, 5169–5176 (2013).
4. Ogden, C. L., Carroll, M. D., Kit, B. K. & Flegal, K. M. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999–2010. *JAMA* **307**, 483–490 (2012).
5. Hagström, H., Stål, P., Hultcrantz, R., Hemmingsson, T. & Andreasson, A. Overweight in late adolescence predicts development of severe liver disease later in life: a 39 years follow-up study. *J. Hepatol.* **65**, 363–368 (2016).
6. Zimmermann, E. *et al.* Body mass index in school-aged children and the risk of routinely diagnosed non-alcoholic fatty liver disease in adulthood: a prospective study based on the Copenhagen School Health Records Register. *BMJ Open* **5**, e006998 (2015).
7. Suomela, E. *et al.* Childhood predictors of adult fatty liver. The Cardiovascular Risk Young Finns Study. *J. Hepatol.* http://dx.doi.org/10.1016/j.jhep.2016.05.020 (2016).
8. Berentzen, T. L., Gamborg, M., Holst, C., Sorensen, T. I. & Baker, J. L. Body mass index in childhood and adult risk of primary liver cancer. *J. Hepatol.* **60**, 325–330 (2014).
9. Hassan, M. M. *et al.* Obesity early in adulthood increases risk but does not affect outcomes of hepatocellular carcinoma. *Gastroenterology* **149**, 119–129 (2015).
10. European Association for the Study of the Liver, European Association for the Study of Diabetes, European Association for the Study of Obesity. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J. Hepatol.* **64**, 1388–1402 (2016).

Competing interests statement
The authors declare no competing interests.

Author biographies
Elisabetta Bugianesi is a Professor of Gastroenterology at the University of Torino, Italy. She is a world-renowned specialist of NAFLD and her research contributed to identify mechanisms of liver damage and related complications. She has published >150 papers with >11,000 citations, and has an *h*-index of 44.
Milena Marietti is a lecturer of Gastroenterology at the University of Torino, Italy. She is part of the research group led by Prof. Bugianesi and is actively involved in clinical investigation of NAFLD.

Subject ontology terms
Health sciences / Gastroenterology / Hepatology / Liver diseases / Non-alcoholic fatty liver disease [URI /692/4020/4021/1607/2750]
Health sciences / Diseases / Nutrition disorders / Obesity [URI /692/699/1702/393]
Health sciences / Risk factors [URI /692/499]
Health sciences / Health care / Disease prevention / Preventive medicine [URI /692/700/459/1748]