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A population-based study of steatosis and fibrosis prevalence in young adults in the UK

Title: Fatty liver disease: putting the spotlight on a silent menace for youngers

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One of the processes that drives the progression to cirrhosis involves fat accumulation in the liver related to either alcohol or obesity, namely alcoholic and non-alcoholic fatty liver disease (AFLD and NAFLD), having identical histological patterns. In the current issue, Abeysekera et al. (1) present an insightful report on the threat of fatty liver disease amongst young adults aged 22-26 year enrolled in The Avon Longitudinal Study of Parents and Children (ALSPAC). One in five of these young participants had a fatty liver, severe in almost half of cases, and one in forty of them had evidence of liver fibrosis. Alcohol intake, even when significant, was not the strongest determinant of steatosis, which was mainly linked to obesity/visceral obesity and to the presence of the metabolic syndrome, hence ultimately attributable to NAFLD. The study has the unquestionable merit of putting the spotlight on the burden of young adults who present with NAFLD; further, it confirms the amplificatory synergy of alcohol and obesity on liver fibrogenesis, while disproving the hypothesis of a beneficial effect of moderate alcohol consumption in NAFLD (2). The strengths of this report are manifold: the large, unbiased, healthy general population cohort and the choice of state-of-the-art, non-invasive tools, to assess steatosis (controlled attenuation parameter-CAP) and fibrosis (transient elastography-TE) at the population level. These results deserve further considerations. End stage liver disease due to NAFLD develops slowly during a lifetime; however, a genetically predisposed background, the earlier exposure to risk factors and other “superimposed hits” (such as alcohol) can increase the risk and/or hasten its progression. Set up in 1991, ALSPAC recruited 14,500 pregnant women from the Bristol area and has been charting their health, plus that of their children ever since. Almost thirty years later, the Children cohort is one the most phenotyped birth cohort in the world. Regretfully, the authors did not explore a wide spectrum of potential risk factors for the future development of NAFLD, such as familial history, birthweight, childhood obesity, sugar consumption, physical activity and longitudinal changes of BMI and alcohol intake across years.
A substantial proportion of the young ALSPAC study participants had already been assessed for NAFLD by ultrasound, with a of 2.5% prevalence in their late teens. The considerable difference 6 years later could be due to the better performance of CAP compared to ultrasound, but changes in body weight or other risk factors during follow-up were not recorded. Major modifications in exposure to alcohol can be anticipated with increasing age, although it can be argued that this is likely a later risk factor compared to obesity. At the age of 24 years, 40% of participants were already overweight or obese. How many of them had already an increased BMI during childhood? Remarkably, early adulthood weight-gain seems to carry a higher risk of mortality than weight-gain in late adulthood. In a large longitudinal Danish study (3), a gain in BMI between 7 and 13 years of age was positively associated with each stage of adult NAFLD, including steatohepatitis and cirrhosis, when adjusted for initial as well as attained BMI. Furthermore, children are often exposed to foods and drinks high in energy, saturated fats, and added sugar (sucrose, fructose and high fructose corn syrup), that could promote steatohepatitis and fibrosis progression independent of total

body fat (4). However, sodas intake is barely taken into account as a risk factor, although it can be as detrimental as alcohol. Lack of physical activity is another neglected but significant contributor (4).

Non-modifiable risk factors can provide the background to hasten the progression of NAFLD: familiar clusters of NAFLD might suggest a genetically predisposed background (namely, PNPLA3 and TM6SF2 variants)(4), while small for gestational age birth weight has been linked to a greater likelihood of NAFLD, probably due to epigenetic regulation in an adverse intrauterine environment (5). In the Cardiovascular Risk in Young Finns Study (6), the childhood predictors of adult NAFLD, 30 years later, were childhood BMI, insulin levels and small for gestational age birth weight.

NAFLD in young adults has clinical implications of utmost importance. A Swedish longitudinal study (7) showed that overweight in late adolescence is a significant predictor of end-stage liver disease almost 40 years later: each unit increase in BMI compared to lean (BMI 18.5–22.5) at the age of 18–20 increased by 5% liver-related outcomes (cirrhosis, decompensated liver disease or liver-related death). With rates of children obesity steadily increasing over time, the message is clear: the threshold of liver-related morbidity, mortality and transplant will be reached at a younger age leading to a substantial additional societal burden. The only “sustainable medicine” is prevention, by tracking and addressing each risk factor for liver disease early in life, starting from parental awareness and promotion of educational programmes, particularly in the schools.

References

1. *A population-based study of steatosis and fibrosis prevalence in young adults in the UK THELANCETGASTROHEP-D-19-00604R3*
2. Dunn W, Sanyal AJ, Brunt EM, Unalp-Arida A, Donohue M, McCullough AJ, et al. 27 Modest alcohol consumption is associated with decreased prevalence of steatohepatitis in 28 patients with non-alcoholic fatty liver disease (NAFLD). J Hepatol. 2012;57(2):384-91.
3. Zimmermann E, Gamborg M, Holst C, Baker JL, Sørensen TI, Berentzen TL. 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. 2015 May 3;5(4):e006998.
4. 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, 2016; 64:1388-1402.
5. Nobili V, Marcellini M, Marchesini G, Manco M, Villani A, Bugianesi E. Intrauterine growth retardation, insulin resistance, and nonalcoholic fatty liver disease in children. Diabetes Care. 2007;30(10):2638-40.
6. Suomela E, Oikonen M, Pitkänen N, Ahola-Olli A, Virtanen J, Parkkola R, et al. Childhood predictors of adult fatty liver. The Cardiovascular Risk in Young Finns Study. J Hepatol. 2016;65(4):784-790.
7. 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. 2016;65:363-368.