

Paediatric Digestive Health Across Europe

Early Nutrition, Liver Disease and Inflammatory Bowel Disease

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INTRODUCTION

United European Gastroenterology (UEG) is committed to raising political and public awareness of digestive health conditions, informing policy makers and encouraging research.

This review highlights the poor quality of paediatric digestive health across Europe, the current state of service provision and the potential impact on longer-term health outcomes and economies.

The opinions of leading gastroenterologists and patient organisations have been canvassed to help identify priority areas for improvement both now and in the future. What is clear, is the urgent need for investment in paediatric digestive health treatments and services, including harmonised training to improve health outcomes.

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Across Europe we have leading paediatric experts and many centres of excellence but these are not widespread and currently cannot meet the needs of children throughout the continent. This has an impact not just on individuals and their families but on society and wider health service provision. UEG hope this report will encourage policy makers, stakeholders and health service providers to adopt the recommendations and prioritise the development of specific paediatric focused strategies for improving the digestive health of children today and for future generations.

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Professor Michael Manns, UEG President

SIX ACTIONS TO DELIVER CHANGE IN PAEDIATRIC DIGESTIVE HEALTH ACROSS EUROPE

Further development and political support for national strategies and public health campaigns to reduce obesity through education, prevention and early intervention Improve and harmonise training and standards through the development of a European paediatric gastroenterology, hepatology and nutrition syllabus

2

Improve subspeciality paediatric GI training and ensure a greater understanding of the complex physical, psychological and social needs of children

3

Develop managed transition and support services as patients move from teenage to adult care

4

Generate and encourage further research into paediatric digestive diseases and early life programming to fully understand the causes of GI conditions, enabling the development of new diagnostic and genetic technology and effective treatment and prevention strategies

5

Further development of specialised centres for the optimal management of children with digestive diseases with long-term follow up, regular reviews and frequent medical interventions by multidisciplinary teams

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EARLY NUTRITION & OBESITY

Incidence

The burden of disease associated with poor nutrition continues to grow throughout Europe.

In 46 European countries one in every three children aged 6-9 years is overweight or obese¹. Childhood obesity is particularly prevalent in Italy and Spain with 35% of 11 year old boys and 22% of 11 year old girls affected². It is increasing at an alarming rate and it is predicted that the global number of children under five who are overweight will rise from the current 41 million to 70 million by 2025 if current trends continue³.





CHILDHOOD OBESITY IS PARTICULARLY PREVALENT IN ITALY AND SPAIN



BEING OVERWEIGHT CAN CAUSE EXTREME ANXIETY AND DEPRESSION



OVERWEIGHT UNDER FIVES WILL RISE FROM 41 MILLION TO 70 MILLION BY 2025

Early nutrition and metabolism can programme the course of the individual's health throughout life. Balanced nutrition in pregnancy, breast feeding and appropriate food choices in early childhood reduce the risk of both rapid weight gain in infancy and of obesity in later life. However. we need to improve our understanding of the detailed mechanisms that mediate these protective effects.

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Professor Berthold Koletzko ESPGHAN President and coordinator of the EarlyNutrition collaborative research programme

Impact

Childhood obesity is linked to many chronic and life threatening diseases including:

- a wide range of functional gastrointestinal diseases⁴
- liver diseases ranging from simple steatosis to cirrhosis, and cancer⁵
- organic GI diseases such as coeliac disease and inflammatory bowel disease⁶
- hypertension and cardiovascular disease
- respiratory and musculoskeletal problems
- type 2 diabetes

The emotional and psychological effects of being overweight include extreme anxiety and depression with severely obese children rating their quality of life as low as that of children with cancer on chemotherapy⁷.

Studies have shown that rapid weight gain during the first two years of life is linked to a markedly increased risk of obesity and related illnesses in later life and obese children are more likely to become obese adults with an associated higher risk of morbidity, disability and premature mortality⁸. Recent research⁹ has established that prenatal nutrition and diet in early childhood not only has a significant effect on growth rates in early life, but exerts a lifelong influence on metabolic and endocrine regulation and associated health outcomes.

The increase in obese children has now reached epidemic proportions and the high cost of treating obesity and related disorders-currently up to 10% of total healthcare costs-threatens the sustainability of public health care systems across Europe⁹.

Current initiatives to tackle childhood obesity

A number of positive strategies aimed at improving diet, service provision, diagnosis and awareness of obesity are in place in a bid to reduce the alarming rise.

These include:

- The European Union (EU), WHO and several European medical scientific associations such as UEG and the European Society of Paediatric Gastroenterology, Hepatology & Nutrition (ESPGHAN) are actively involved in a range of programmes to raise awareness of obesity as a disease and its prevention. These programmes offer greater understanding about metabolic programming, essential for aiming to meet the World Health Assembly's target of halting the increase of childhood obesity by 2025.
- The new EarlyNutrition Academy and e-learning facility established in collaboration with ESPGHAN and their harmonised training syllabus for paediatric gastroenterology, hepatology and nutrition have helped to significantly improve training and harmonise standards across Europe for subspecialty training.
- The largest research-related EU initiative currently investigating the prevention of obesity through nutritional programming effects in

pregnancy and early childhood is the global EarlyNutrition collaborative research programme. The five year project anticipated for completion in 2017, with a budget of nearly €11 million, aims to analyse a wide variety of metabolic factors and genetic modifications that may be involved in the process of early metabolic programming of lifelong health, helping to identify the key molecules that mediate links between nutrition and growth rate.

As part of this research programme, simple low-cost early interventions have shown marked benefits of preventing children's risk of obesity. Structured counselling of pregnant women with advice about diet and physical activity reduced birth weight of more than 4kg by approximately one fifth. Birth weight above 4kg has been shown to double the risk of obesity¹⁰, therefore these simple interventions, including three counselling sessions and three telephone calls, have resulted in significant preventative benefits¹¹. This research programme also highlights that early environment and nutrition during sensitive phases of development plasticity in pregnancy and early childhood can affect the process of epigenetic modification. These modifications can in turn alter organ function and influence one's lifetime risk of various disease conditions. These results throw new light on key questions concerning the regulation of growth during early childhood, and help to frame wellfounded recommendations for early nutrition practice.

• The EU Childhood Obesity Project (CHOP) identified that infants fed formula milk with a low protein content-closer to that of breast milk-weighed significantly less than those on higher protein formula. These differences persisted over time. By this simple improvement of infant feeding, the risk of obesity at school age was 2.5 fold reduced¹².

We are born with practically sterile guts, which are then colonised for life with the bacteria from our mothers, that stay with us for life. The first two years of childhood are critical for establishing bacterial colonisation and future gastrointestinal health. These early events may be vital in preventing IBD, IBS and other inflammatory conditions, as well as obesity.

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Professor Berthold Koletzko ESPGHAN President and coordinator of the EarlyNutrition collaborative research programme

MORE LIKELY TO OVERCOME LIFE THREATENING CHILDHOOD DISEASES WITH THE RIGHT NUTRITION

Recommendations for improving nutrition and tackling childhood obesity

Early nutrition and obesity needs serious attention and urgent action to ensure that the EU Commission's goal to halt the increase in childhood obesity by 2020 is met.

The following measures are recommended to help achieve this goal:

- Further development of national strategies for healthy nutrition education, prevention and early intervention
- Political support to improve and harmonise training and standards and the development of a European paediatric gastroenterology, hepatology and nutrition syllabus to ensure high quality provision across Europe
- Subspeciality paediatric Gl training and a greater understanding of the complex physical, psychological and social needs of children

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The economic burden of treating adult obesity is just too great for the European region and priorities need to change quickly. With growing evidence of the link between early nutrition and lifestyle and obesity, and digestive health in general, we must prioritise research into the underlying mechanisms and focus our resources and training on prevention strategies.

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Professor Herbert Tilg

UEG Scientific Committee and Professor and Director of the Division of Endocrinology, Gastroenterology and Metabolism, Innsbruck Medical University

PAEDIATRIC INFLAMMATORY BOWEL DISEASE (PIBD)

Incidence

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory disorders of the gastrointestinal tract, collectively known as inflammatory bowel disease (IBD).

According to the United European Gastroenterology (UEG) Survey of Digestive Health across Europe¹³:

- up to one in four cases of IBD are diagnosed during childhood
- childhood onset IBD accounts for 20-30% of all IBD cases
- incidence has been steadily increasing over the last few decades
- highest reported incidence of Crohn's disease reported in Sweden, Norway and Hungary and ulcerative colitis in France, Finland and Hungary
- childhood onset IBD presents different challenges for the patient and the gastroenterologist

There is no solitary cause of IBD but it is thought to be due to a combination of genetic and environmental factors. A study based on data in the Danish National Patient Register found that the children, siblings or parents of individuals with IBD had an eightfold increased risk of developing the disease¹⁴.

Extensive research highlights the role intestinal microbiota play in the development of IBD. The well-known 'hygiene hypothesis' suggests that a cleaner environment, smaller families and lower exposure to farm animals increase the risk of IBD and other immune-mediated and inflammatory diseases in westernised nations^{15,16}.

The period immediately pre and post birth as well as early life events, including antibiotic use, may also play a significant role in the development of IBD¹⁷.

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Paediatric IBD is increasing in incidence and severity and provision needs to be improved with more consistent treatment practices to improve the outlook for young people with IBD across Europe, many of whom suffer well into adulthood.

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Professor Gigi Veereman UEG Public Affairs Committee and Consultant in Paediatric Gastroenterology and Nutrition at the Free University, Brussels



It is vital that the transition from paediatric to adult care is handled properly as this is such a challenging time for a young adult and their family. It is welldocumented that children with GI conditions who are not managed properly have a high incidence of psychosocial morbidity in adulthood.

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Dr. Nikhil Thapar

Consultant Paediatric Gastroenterologist and chair of the European Society of Paediatric Gastroenterology, Hepatology & Nutrition

52% FELT THAT IBD HAD NEGATIVELY AFFECTED THEIR EDUCATION

Impact

Paediatric gastroenterologists treating PIBD face many challenges, with the majority being linked to the differences in diagnosing and treating IBD in children compared with adults.

IBD can be extremely debilitating and patients with IBD may also have a higher risk of developing small bowel cancer and colorectal cancer (CRC), with research indicating that IBD patients are six times more likely than the general population to develop CRC¹⁸. In fact, CRC accounts for approximately 10-15% of all deaths among IBD patients¹⁹. Complications in adult life may also include osteoporosis and infertility. In addition, traditional adult based therapies can have a potentially negative effect on the developing body, for example the impact of corticosteroid therapy on bone density²⁰.

Children with IBD often present with a more severe form of the disease than adults and a more aggressive disease course which can have a devastating effect on their quality of life, as well as their education and career prospects. The recent European IMPACT survey, carried out by the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA), assessing the burden of IBD in Europe, revealed that 52% felt that IBD had negatively affected their education²¹.

The same survey also highlights alarming delays in diagnosis of up to 5 years for 18% of under 18's²². These delays as well as the debilitating symptoms can have a significant impact on a child's emotional and mental health, with many found to have behaviour problems, psychiatric disorders and severe psychosocial issues²³.

Not only does this present huge emotional costs to the patient and their family but CD and UC also create a considerable economic burden to health care systems and society.

Current initiatives to tackle PIBD

Initiatives aimed at improving patient outcomes and service delivery in PIBD include:

- The recently created global paediatric IBD network (PIBDnet) allows the initiation of academic multicenter studies over Europe and beyond. PIBDnet aims to advance the care of children with IBD globally through investigator and industry initiated research, the development of optimal treatment plans, and by monitoring safety and effectiveness of current and emerging treatments²⁴. The recent PIBDnet initiated and Horizon 2020 funded project PIBD-SETQuality provides a unique chance to advance the care of patients with PIBD all over Europe and it is an exciting opportunity to see the benefits of collaborative work in the area of IBD. It will help to measure the impact and severity of the disease on the individual but will also look at social outcomes and cost-effective ways of treating patients in the community, thus improving the care of PIBD for future generations.
- A clinical trials network to study effective medicines for paediatric patients in the speciality of Gastroenterology, Hepatology and Nutrition, set up by the Paediatric European Digestive Diseases Clinical

Research Network (PEDDCReN), with support from UEG and in collaboration with national gastroenterology societies as well as PIBDnet.

- A consensus statement from the European Crohn's and Colitis Organisation (ECCO) of critical factors for the optimal conduct of paediatric IBD trials, highlighting the importance of steroid-free mucosal healing as the primary outcome measure for all new drugs and that paediatric trials must be performed early in the development of new drugs in order to reduce current off-label use of IBD medication in children²⁵.
- New management guidelines and consensus statements by the Paediatric IBD Porto Group, a group of 30 paediatric IBD experts from ESPGHAN, covering the use of biosimilars and endoscopy in paediatric IBD as well as surgery and post-operative care in Crohn's disease. The Group is also conducting collaborative research, including ongoing registries and establishing more precise predictive tools, leading the way in improving current diagnosis and treatment of children with IBD.

- The first set of paediatric specific guidelines²⁶ – the Paris Classification – developed by ECCO, in partnership with ESPGHAN, is a welcome step forward in the process of assessing the specific needs of paediatric IBD service delivery through providing a clearer definition about characteristics unique to paediatric-onset IBD enabling a more tailored treatment approach.
- New research highlighting the link between early life and immunity, the role of vaccinations in preventing IBD, the benefits of early treatment with immunomodulators and the benefits of exclusive enteral nutrition (EEN). EEN has recently been recommended in the new ECCO and ESPGHAN guidelines for the management of PIBD as a first-choice agent to induce remission and is considered by many gastroenterologists as an exciting advance in the treatment of PIBD. This has an excellent safety profile which can alter the evolution of the disease, with changes seen in antiinflammatory markers within just a couple of days.

There is an urgent need for further investment in clinical research dedicated to PIBD, and the development of a specific research programme, if the increase in incidence continues at the current pace.

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Professor Frank Ruemmele, MD, PhD President of PIBDnet and GETAID pédiatrique Professor of Pediatrics Université Sorbonne Paris Cité, Paris-Descartes, Paris Hôpital Necker Enfants Malades, Service de Gastroenterologie pédiatrique Institut

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In our practice we aim to start a gradual transition of every child from the age of 13 years into 'handover clinics' run jointly by paediatric and adolescent IBD doctors and it is my hope that this model can be rolled out across Europe to improve the provision at this transitional stage, and prevent children getting 'lost' in the system.

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Dr Nikhil Thapar

Consultant Paediatric Gastroenterologist and chair of the Gastroenterology Committee of the European society of Paediatric Gastroenterology, Hepatology & Nutrition

Future recommendations for PIBD

Advances have been made in the treatment of PIBD across Europe with new guidelines, training syllabi, research and the PIBDnet registry. However, to halt the increase in the incidence and the impact and severity of the disease, further action needs to be taken including:

- Greater understanding of the complex physical, psychological and social needs of children with PIBD
- Tailored care and services, including the transitional period into adult services, which are key to improving the patient's experience and ensuring successful disease management.
- Funding to provide more extensive subspecialty paediatric GI training to meet the requirements of new guidelines
- Further research into all types of IBD, not just UC and CD, to fully understand the causes enabling the development of effective treatments and prevention strategies
- Further research into early life programming to understand the causes and enable the development of immune-mediated GI conditions and facilitate the development of advanced treatment and prevention strategies
- Long-term follow up, regular reviews and frequent medical interventions by multi-disciplinary teams
- Significant reductions in the delay between adult trials of new treatment and those in children to ensure that new appropriately formulated licensed treatments with proven safety profiles are available for children as soon as possible

PAEDIATRIC LIVER DISEASE

Incidence

Liver disease is becoming increasingly common in young children, with chronic liver diseases in children representing a rising problem with significant impact on public health. Several paediatric liver diseases, including viral hepatitis B and C and metabolic syndromes related to obesity and being overweight, are the leading causes of cirrhosis and primary liver cancer in Europe.

Non-alcoholic fatty liver disease (NAFLD) is the term used to describe fat build-up in liver cells in people who do not drink alcohol excessively. NAFLD is rapidly becoming the most common liver disease worldwide and is the most common persistent liver disorder in Western countries. Over the past few decades (NAFLD) has become the most common cause of chronic liver disease among children and adolescents in Western countries, with cases documented in children as young as 3 years old²⁷.

NAFLD prevalence continues to rise among paediatric patients affecting up to 10% of Europe's paediatric population, with a higher incidence in boys²⁸. Obesity presents a major risk factor for NAFLD, with German and Italian studies showing a high prevalence (up to 44%) of NAFLD in obese children²⁹. Increases in the obesity epidemic are expected to result in substantial increases in NAFLD prevalence in the future³⁰.

Hepatitis B virus (HBV) is transmitted from mother to baby through contact with infected blood or other body fluids. Although the incidence of HBV infection has dramatically declined since the implementation of universal immunisation programmes in several countries and blood-donor screening, a significant number of children are still infected each year, often developing chronic infection which can lead to cirrhosis and liver cancer. Mother to child transmission accounts for more than 50% of chronic infections in highly endemic areas, with the risk of chronic infection higher in newborns (90%), infants and children under 5 years (25-30%) than for adolescents or adults (<5%)³¹.

In the EU, the hepatitis C virus (HCV) is unfortunately showing a significant increasing trend with the number of newly reported cases per 100,000 population increasing from 4.3 cases in 1995 to 6.9 cases in 2007. A higher prevalence is recorded in southern Europe, including Italy, Romania and Spain, medium prevalence in Bulgaria, France, Greece and Poland and the lowest prevalence reported in Belgium, Germany, the Netherlands, Sweden and the UK³².

Insufficient screening of transfusions, unsterilised medical equipment and reused needles and syringes continue to be the major routes of HCV transmission in developing countries, whereas vertical transmission, from an infected mother to her unborn or newborn baby and drug abuse in young adults, are the major routes in developed countries. Vertical transmission is now the main source of infection in children and is less than 10%³³. Hepatitis C is often asymptomatic, and symptoms may not appear until the liver is severely damaged³⁴.



MORE THAN 50% OF CHRONIC HBV TRANSMISSIONS FROM MOTHER TO CHILD TRANSMISSION



HIGH PREVALENCE (UP TO 44%) OF NAFLD IN OBESE CHILDREN

CHRONIC INFECTION OF HBV OCCURS IN UP TO 90% OF CHILDREN INFECTED AT BIRTH

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Most paediatric liver diseases need a lifetime of care which carries a significant cost burden for our healthcare systems. As a result, it is not always possible to provide the ideal care for children and many children get lost from the system and suffer as a result.

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Professor Michael Manns

UEG President and Director of the Department of Gastroenterology, Hepatology and Endocrinology at the Medical School of Hannover

Impact

The main future morbidity and mortality of children with NAFLD is from type 2 diabetes, atherosclerosis or end stage liver failure. Currently there is no method of accurately assessing the stage of the disease apart from taking a biopsy and management of the disease focuses largely on weightloss programmes through a combination of diet and exercise³⁵.

The risk of developing chronic hepatitis B infection depends on the age at which infection is acquired. Chronic infection occurs in up to 90% of children who acquire the infection at birth but occurs in less than 10% of people infected as adults³⁶.

If left untreated, hepatitis C carries a significant risk of cirrhosis and liver cancer. Impaired quality of life, potentially severe enough to have a negative effect on learning, has also been reported in children with chronic HCV infection, including developmental delay and learning disorders³⁷.

New initiatives and developments in the management of paediatric liver disease

Initiatives aimed at improving patient outcomes and service delivery in paediatric liver disease include:

- An exciting new initiative to improve the management of paediatric GI across Europe-European Reference Network Paediatric Liver Centres-is being developed with the European Association for the Study of the Liver (EASL). If successful, this initiative will ensure that accredited centres are available across Europe for hepatic disease, to facilitate research from 'the cradle to the grave' and a comprehensive body of research to ensure a life-time of optimal care for patients with liver disease. Currently, many European countries have excellent specialist centres but transition to adult services, essential for paediatric liver diseases, is poor.
- It is now widely recommended that every obese child or adolescent should have their liver enzymes checked to ensure the earliest possible diagnosis of NAFLD. The child may then be referred for confirmation of diagnosis, most commonly via liver ultrasound, to verify accumulation of fat in the liver. Liver biopsy is the current gold standard for the diagnosis of NAFLD and the only procedure currently available to assess

whether a child with NAFLD has the more serious condition non-alcoholic steatohepatitis (NASH)³⁸.

- Development of a new paediatric specific grading score for NAFLD has significantly improved a paediatric gastroenterologist's and hepatologist's method of interpreting liver histology in paediatric cases of NAFLD and NASH.
- Most EU and EEA countries now have a surveillance system for HBV and HCV infections. However, due to differences in system structures, reporting practices, data collection methods and case definitions used, the surveillance data is difficult to compare across countries. For example, in 14 countries there was one specific surveillance system whilst 15 countries indicated that they use multiple surveillance systems to monitor hepatitis C. Eleven countries indicated that they have implemented the EU-2008 case definition yet four countries apply the EU-2002 case definition. There is also screening for hepatitis B in pregnancy in 24 countries but only 2 antenatal screening programmes for hepatitis C in the EU/EEA³⁹.
- New clinical practice guidelines for the management of hepatitis B in children by ESPGHAN highlight the importance of regular follow-up visits to evaluate the need for various treatments. They recommend full blood counts and liver function tests to be performed yearly and liver cancer surveillance with ultrasound to be carried out every 6-12 months, depending on the stage of fibrosis. It is also noted in the guidelines that a liver biopsy remains the most effective method to evaluate the relevant treatment strategy but new non-invasive methods, such as FibroScan, could prove useful in future to avoid liver biopsy, particularly during follow-up visits40.
- Universal HBV immunisation programmes. These are adopted in 47 out of 53 countries in the WHO European region, creating a generation of children and young adults with virtually no markers of HBV infection. Six countries (Iceland, United Kingdom, Denmark, Norway, Sweden and Finland) have not employed universal immunisation and only target people who are at risk, which is more challenging to implement than the universal approach⁴¹.

The fundamental issues for the future to prevent certain paediatric liver diseases and improve treatment outcomes include, firstly, developing genetic technology to speed up diagnosis and facilitate the development of more targeted treatments. Secondly, we need to improve the long-term management of children with liver disease and, lastly, we must harness the enthusiasm for collaboration across Europe to facilitate optimal treatment management and outcomes. Funding is therefore vital to enable progress and essential advancement of the management of paediatric liver disease across Europe, to ensure that these children lead full and active lives well into their eighties.

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Professor Deirdre Kelly Professor of Paediatric Hepatology at Birmingham's Children Hospital

Future recommendations for the management of paediatric liver disease

Liver disease is increasingly common in young children and involves a lifetime of care. Further investment is required to reduce incidence, improve diagnosis and to establish an infrastructure that offers seamless support and management from paediatric to adult service provision.

Key recommendations include:

- Primary non-invasive evaluation using biochemical parameters, imaging tests and serum biomarkers as initial tools to confirm the diagnosis of fatty liver disease
- Development of genetic technology to speed up diagnosis and facilitate the development of more targeted treatments
- Further research to evaluate the use of oral direct acting antivirals for children
- Further development of vaccines for HCV infection and a universal vaccination for HBV infection

- Specialised centres for the optimal management of children with chronic liver disease
- Appropriate public health and education campaigns, implemented through schools, to halt the rise of HCV infection in Europe
- Harmonised screening programmes for at risk groups, hard-to-reach populations, and the general population
- A multidisciplinary approach to Europe-wide research, specialist training and paediatric patient management

SUMMARY

This comprehensive review of paediatric gastroenterology outlines many exciting initiatives and strategies that are in place across Europe but it also highlights many areas of concern that require urgent action and change for the benefit of paediatric patients.

It is vital that work continues in order to halt the alarming rise in obesity and reduce the long-term impact on health and society through improved nutrition and raised awareness of the impact of childhood obesity.

New networks, registries, guidelines and research, designed to reduce the impact of paediatric IBD need to be supported by investment to ensure more extensive sub-speciality training and on-going physical and psychological support for paediatric patients.

Non-alcoholic fatty liver disease now affects 10% of Europe's paediatric population and urgent action is needed to improve screening and vaccination programmes to halt the alarming increase in incidence.

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We hope that the issues UEG has highlighted in this review will initiate an increased focus on improving paediatric gastroenterology services throughout Europe to ensure all children have access to a healthy diet, specialist services and follow-up care helping to minimise the risk and burden of long-term GI problems.

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Professor Paul Fockens UEG Vice President

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