ERAB

THE EUROPEAN FOUNDATION FOR ALCOHOL RESEARCH

2003 -2022

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Dedication

This publication is dedicated to Dr. David Long MBE (1949 – 2021). David was a friend and colleague for more than two decades. He was instrumental in the foundation of ERAB and an active supporter throughout its life. He died suddenly during the preparation of this text.

Acknowledgements

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- All the brewers and Brewing Trade Associations who sponsored ERAB; and
- The Brewers of Europe for having the vision to create ERAB and support it for so many years.

Janet Witheridge

An electronic version with links to all the publications can be downloaded from www.erab.org/publications.

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Introduction

Background to the Organisation

The European Foundation for Alcohol Research (ERAB) was active between 2003 and 2021. It was established in order to support independent research into the effects of alcohol in general, and beer in particular, on human health and behaviour. The remit of the Foundation also covered the prevention and treatment of problems arising from the inappropriate consumption of alcohol.

ERAB was funded exclusively by the European Brewing Sector[1]. The fundamental principle on which ERAB was founded was its unassailable independence from those providing the funding. Crucially, brewers were precluded from influencing the selection or direction of research projects. Together with robust peer-review, this protected the credibility of the research outputs and therefore the unquestionable value to others in the scientific community, those developing public health policy, the alcoholic beverage sector and the general public.

The foundation of ERAB represented an important milestone in the long-term evolution of collaboration between industry and academia in promoting independent research. This collaboration had commenced in North America, driven by the need to gain a greater understanding of how products such as beer and other alcoholic beverages affect the health of society.

ERAB has been a key player in the brewing sector's efforts around the world to promote scientific knowledge in this vitally important field of endeavour which started over fifty years ago.

1 ERAB was funded by The Brewers of Europe, the European association for 29 national brewer trade associations, all the national brewing trade associations who were their members and the leading five European brewing companies - InBev, Carlsberg, Heineken, SABMiller and Scottish and Newcastle. Takeovers and mergers reduced these five companies to four (Anheuser-Bush InBev nv/sa, Carlsberg Breweries A/S, Heineken International BV, Asahi CE & Europe Services sro.

A Short History of Brewing Sector Sponsorship of Alcohol and Public Health Research

Early Links Between Industry and Academia

In 1969, following a food safety issue associated with the use of cobalt salts as a permitted additive in the production of beer, brewing organisations in the USA and Canada sought urgent scientific guidance. Although it was never unequivocally proved to be the causative agent, the use of cobalt was associated with a large number of cases of a rare disease syndrome involving inflammation of the heart muscle. To avoid future unforeseen health scares, the US Brewers Association (now the Beer Institute) requested the assistance of a group of physicians and scientists under the chairmanship of Professor Thomas B Turner (then the newly retired dean of the medical school, Johns Hopkins University) to provide advice on all potential food safety and toxicological issues associated with the brewing process. The resultant comprehensive review concluded that, of all potential toxicants, the impact of ethanol itself on health should be the primary consideration for the brewing sector. As a consequence, thereafter, the medical groups advising brewers in North America focussed research on the health and socio-behavioural effects of alcohol consumption.

Information exchange

At that time there was a burgeoning interest amongst brewing organisations in other parts of the World about the health impacts of alcohol. This was being addressed through the establishment of similar medical advisory groups. Colleagues from the UK, including Dr. Alan Leach from the Brewers' Society, (now the British Beer and Pub Association) and senior medical advisors[2] were engaged in these endeavours, working initially as medical advisors to the Brewers' Society. Similar Groups were formed in Canada and Australia and New Zealand.

2 Including Professors Sir Hedley Atkins, Sir Cyril Clark, Sir Theo Crawford and later, Sir Douglas Black, Sir Christopher Booth, Sir Philip Randle, Walter Sommerville and Tom Meade.

Research efforts were greatly enhanced by the ready exchange of scientific knowledge between countries. This free-flow of information was promoted through conferences held every year and rotated between the US, UK, Canada and Australia. In each case the meetings were sponsored by the host brewing trade association. These meetings became known as the International Medical Advisory Group (IMAG) conferences. Presentations were made by the advisors and invitees who were expert in various scientific disciplines. Representatives from the brewing sector, particularly the scientists concerned with brewing technology, also attended and participated in these scientific exchanges. Such dialogue generated a unique body of knowledge concerning the hitherto unexplored centre-ground between medical and brewing science.

Safeguarding the Credibility of Industry-Sponsored Research

Many of the medical advisors recognised that very little data existed about the impacts on health and behaviour of moderate exposure to alcohol, although this was the manner in which most alcoholic beverages were consumed in practice. The common paradigm for research in the field of alcohol studies was to identify problems that resulted from excessive consumption and to explore the resultant disorders, in detail, to determine whether specific medications could be used to treat them.

Recognising that this novel approach, involving moderate exposure to alcohol, would require a new body of knowledge, they recommended that the brewing industry provide modest funding to investigators such as Dr. Arthur Klatsky, whose pioneering work was on studying risk factors for coronary heart disease. His research led to the elucidation of the now familiar, "J-shaped curve", (i.e. there is a lower mortality risk amongst those who drink in moderation as compared with abstainers or heavy drinkers, mainly due to a lower incidence of cardiovascular disease in moderate drinkers). This observation introduced a new perspective. As well as health risks, there were also potential benefits to health associated with the consumption of alcoholic beverages in moderation. Evaluating the delicate balance between health risks and benefits has presented an ongoing challenge to research scientists.

In pursuing this approach, the medical advisors to the US Brewers Association recognised that there could be a perceived conflict of interests if the brewers were to fund such research directly. They therefore recommended that the brewing sector create a separate and independent, non-profit making foundation that would ensure an arms-length relationship between the investigator and the brewing industry.

Following lengthy discussions, the medical advisory groups in the US and Canada were merged in 1982 to become the wholly independent Alcoholic Beverage Medical Research Foundation (later known as ABMRF: The Foundation for Alcohol Research) to award funding in these fields of research.

From its inception, the ABMRF operated as a charitable trust to encourage investigator-initiated research proposals that were reviewed by independent panels of scientists utilising guidelines for review established by the National Institutes of Health in the US. Furthermore, the investigators were encouraged to publish their findings without any prior review by ABMRF. The principle of utilizing peer-review to separate the source of funding (the brewing sector) from the decisions about which applications to fund was an essential element to ensure the integrity of research findings. This fundamental principle also became the foundation stone for ERAB.

The Establishment of ERAB

Historically, the UK was the only European country to be a participant in the IMAG conferences. The UK trade body, the Brewers' Society (now the British Beer and Pub Association) funded medical research projects throughout the 1980's and 1990's after peer review had been obtained through a network of medical and scientific advisors.

Some considered it anomalous that, whereas medical advisors to UK-based brewers were in ongoing dialogue with those in North America and Australasia, mainland Europe was not involved. This was partially addressed in 1997 by the invitation of Count Rodolphe de Looz-Corswarem, Secretary-General of the CBMC (now The Brewers of Europe) to attend IMAG conferences. In the margins of these meetings, numerous discussions were held principally between the Secretary-General of the CBMC, the President of ABMRF (Dr. Mack Mitchell), and the British Beer and Pub Association (Dr. David Long) to explore how there might be a coordinated

involvement of medical advisors across Europe in the work of IMAG. The logic of such a development was consistent with the fact that the brewing companies were becoming increasingly internationalised through a series of mergers and consolidation. Several of the companies who supported the medical advisory group in the UK had established headquarters in Europe.

In 2000, the CBMC commenced serious discussions on establishing a European Research Advisory Board. These detailed discussions were led by Count Rodolphe de Looz-Corswarem, Paul Bergqvist, President of the CBMC, Professor Oliver James, dean of the medical faculty of the University of Newcastle Upon Tyne and Dr. David Long. Consideration was given to merging the new group with ABMRF but, for a variety of reasons, the organisers felt that a separate body based in Europe would have greater resonance with the European research community. In 2002 Piero Peron, succeeded Paul Bergqvist as President and he finalised the agreement to set up ERAB and approached Raymond Georis, Chairman of the European Foundation Centre with a view to the Chairmanship.

Developing the Role of ERAB in Public Health Research

The annual IMAG conference in 2002 (the 30th) was hosted by the UK Medical Advisory Group in Brussels to include scientists from across Europe and to encourage the establishment of the European Research Advisory Board as a distinct organisation. The honourable David Byrne, European Commissioner for Health and Consumer Protection, opened the IMAG conference by challenging the delegates to complete the formation of ERAB, stressing that issues related to alcohol were among priorities on the agenda for public health in EU Member States.

In his opening remarks to the conference, Professor Oliver James recognised ABMRF as being an excellent example of an appropriate, healthy relationship between the industry and academia, one that differed markedly from that of the tobacco industry. Dr. Mack Mitchell Jr., President of the ABMRF, emphasized the need to avoid even an apparent conflict of interest between those funding the organisation and decisions regarding which projects to support. With regard to the difficult subject of balancing risks and benefits, it was essential to have a thorough appreciation of both. In his view, funding this research was ‘good business’ for

the brewing sector: to invest in a better understanding of the consumption of alcohol and prevent its misuse; to address critical problems facing society; and to participate actively in solving those problems.

These presentations were the catalyst for further detailed discussions and within a month the heads of delegation of the CBMC, which had now become The Brewers of Europe, had drafted a business plan for ERAB that committed funding of € 500,000/annum for an initial period of three years.

ERAB was established as a foundation of public utility under Belgian law, independent of, but financed by, The Brewers of Europe through contributions from its member trade associations and four major breweries. The three founding directors, Professor Oliver James, Raymond Georis and Piero Perron, President of The Brewers of Europe, guided the preparation of by-laws, the recruitment of an Advisory Board and Board of Directors and ancillary tasks required to complete the establishment of the ERAB as a separate foundation. Mrs Janet Witheridge was appointed Secretary-General and, has steered the Foundation throughout its entire existence.

Availability of funding for research grants was announced in major European journals in February 2003. The founders of ERAB were careful to ensure representation of the public interest by requiring a majority of the Board to be public members with only a minority of members appointed from the brewing sector. A list of all Directors and Advisors is included in Annex 1.

The 34th IMAG conference was held in Copenhagen in October 2006. The scientific programme was planned by ERAB and hosted by The Brewers of Europe with assistance from Carlsberg and the Danish Brewers Association (Bryggeriforeningen). One of the sessions was chaired by Robert Madelin, Director-General of the European Commission's department for Health and Consumer Protection. This occasion represented the first European conference since the foundation of ERAB. Twelve ERAB grantees presented their research findings. At the next ERAB-organised IMAG, (36th, held in Frascati, Italy in 2010) the majority of speakers were presenting research funded by ERAB. ERAB continued to organise IMAG conferences every 4 years. In 2014 (28th), it was held in Amsterdam, the Netherlands and the title was changed to the International Meeting on Alcohol and Global health, retaining the Acronym but giving a better reflection of its content. In 2018 (39th), the last IMAG conference was held in Leuven, Belgium. A full listing of IMAG conferences appears in Annex 2.

Nurturing Young Scientific Talent

A fundamental objective of ERAB was to encourage young scientists to work in the field of alcohol research. To this end, as well as providing major research grants, ERAB also offered a number of travel grants and exchange awards for researchers under the age of 35. The travel awards enabled young scientists to travel to conferences to present their research findings. The exchange awards allowed periods of study/collaboration in centres of excellence anywhere in the world. In addition, small awards were made available to help publish relevant PhD theses. These various strands of financial support proved to be very successful in attracting new talent and seeding novel ideas in the field of alcohol research. More details of ERAB awards and collaborations appear in Annex 3.

Collaborative Research Between ERAB and ABMRF

In 2010, ERAB took a bold step in forming a strategic partnership with ABMRF to answer a call from DG (Directorate General) RELEX [3] to coordinate a review of underage drinking in Europe and North America. Although the application was unsuccessful, it reinforced a belief that the two bodies were ideally placed to deliver such a project in order to generate strategy options to assist authorities in Europe and North America to address this important public health issue. A modified version of the original application was proposed, additional funding was provided at arms-length by the brewers and work commenced in 2011.

This collaborative project marked a new direction for ERAB. Previously open calls had been issued for grant applications with successful awards being based on the quality of the science as judged by peer-review. This special project was no less independent but constituted a review of the existing evidence-base in a particular area, (in this case underage drinking), rather than initiating new research. As normal, the work was subject to peer review and funding was provided at arm's length by the brewing sector.

3 DG RELEX, now the European External Action Service (EEAS), the European Union's Diplomatic arm, was the Unit within the European Commission with responsibility for External Relations with other countries of the world including the US and Canada.

The experts involved[4] were from both continents and were able to draw meaningful comparisons and make recommendations on effective interventions in different situations based on the evidence reviewed. The literature review was focussed on the second decade of life. It led the collaborators to provide a suite of recommendations aimed at delaying the age of onset of drinking and preventing heavy episodic (binge) drinking in this age group.

This departure from the normal *modus operandi* of both the ERAB and ABMRF proved to be of enormous value in generating a transatlantic dialogue on this common problem area, and in providing an expert assessment of different initiatives which could be effectively employed by the authorities. The outputs were published in an E book; '*Underage Drinking, A Report on Drinking in the Second Decade of Life in Europe and North America*'. Further detail is included in Annex 4.

The report was also presented to an invited audience on 27th November 2012 in the European Parliament in Brussels, Belgium with the support of Markus Ferber MEP, a member of the ERAB Board of Directors. Dr. Michael Hübel, Head of Unit - Health Determinants, DG SANCO, joined several of the report authors to introduce the review findings and the report recommendations. He welcomed the publication in the context of EU action on alcohol-related harm. The audience included Members of the European Parliament and other Commission departments.

Initiatives to Enhance the Impact of ERAB

By its tenth anniversary, ERAB had become firmly established as a unique private foundation fostering research to understand the effects of alcohol on health and behaviour. In 2012, ERAB was officially recognised as an Institution of Scientific Research by the Belgian Minister of Finance and was accepted by the King Baudouin Foundation to be part of the Transnational Giving Europe Partnership Network.

Research outputs were appearing regularly in high quality peer-reviewed scientific journals. Communication channels were firmly established through the IMAG

4 EDITORS: Philippe De Witte, Belgium, EU, Mack C Mitchell, Jr., USA
AUTHORS: Franca Beccaria, Italy, EU, Patricia J Conrod, Canada, Kim Fromme, USA, Antti Latvala, Finland, EU, Sherry H Stewart, Canada, Reinout W Wiers, The Netherlands (EU), Helene R White, (Chair), USA.

conferences, an annual report, newsletters circulated to a network of recipients in the scientific community, a website and publication of a book in 2010; *'New Frontiers in Alcohol and Health'*. More detail is included in Annex 4.

The number of applications being received grew each year and even with annual funding of € 500,000, it was only possible to support a fraction of the high-quality project applications. Those involved in the operation of ERAB became concerned about the project-funding shortfall. They felt constrained in their ambition to enhance the impact of ERAB and the aspiration for it to become the foremost authority in this important area of public health.

It was becoming apparent that the funding model would need to evolve if ERAB were to extend its research base. Brewing companies continued to consolidate and become more internationalised. Many had their own in-house expertise and well-developed research programmes. The conclusion reached was that for ERAB to realise its ambition to support a greater proportion of grant applications, additional funding from outside the brewing sector would be required.

The successful joint ERAB/ABMRF initiative on underage drinking, identifying health strategy options, pointed to the potential to attract external funding from the European Commission and/or the WHO. However, it was acknowledged that the lead time involved in securing such funding would be considerable.

It was recognised that the challenges of alcohol consumption impacted other industrial sectors. It was considered that they might be amenable to collaborative funding of the research programme, particularly because of the established ERAB *modus operandi* guaranteeing independence and therefore the validity of the research outputs. In 2016, under the chairmanship of Emeritus Professor Frans Kok, then Chairman of the Board of Directors, a Joint Funding Task Force was established. It identified the following five potential funding streams: major companies; foundations/charities; brewing-related organisations; EU co-funding; and, donations. A pre-proposal scheme for applications was also introduced in order to reduce the administrative burden on applicants and ensure that only those with a realistic chance of success were asked to complete a full application.

Although there was an expression of interest from a number of potential collaborators, this, unfortunately, did not result in enhanced funding of the ERAB research programme.

A Focus on Beer and Health Research

As mentioned above, the catalyst for medical research on alcohol funded by the North American brewers had been the recognition that there was a knowledge-gap, specifically around beer and health issues. The continuing need for ERAB to include the specificities of beer in its own research programme was recognised in the By-Laws. Fundamentally, ERAB was *'to promote scientific knowledge of… alcoholic beverages in general, and beer in particular'*. Historically, there had been relatively few research applications relating specifically to beer, and the quality was generally low when compared with the bio-medical and psycho-social project applications.

In order to address this shortcoming, ERAB reached out to the European Brewery Convention (EBC), The Brewers of Europe's division responsible for promoting scientific excellence in the brewing sector, to explore the potential for promoting joint projects. ERAB and EBC held three annual joint meetings for brewing scientists and biomedical experts to discuss common ground between their distinct areas of interest and to explore the potential for collaborative projects.

The two organisations then agreed that there would be scientific merit in jointly funding a new grant to support beer and health research. An ERAB/EBC Advisory Board was established in 2018 with a mandate to assess pre-proposal applications for the new grant and decide which should be invited to complete a full application, organise external reviews and decide which application should be funded based on the results of the reviews.

In practice, the large number of high-quality pre-proposals was gratifying. A short-list of five was agreed and the applicants were invited to submit full proposals for consideration. The successful project (see page 129) was announced at the IMAG conference in September 2018. The winner was a co-application by Claus Hellerbrand (Erlangen, Germany) and Ina Bergheim (Vienna, Austria) for their research project on "Analysis of the synergistic anti-inflammatory effect of the hop derived beer compound iso-alpha-acids and xanthohumol".

Ending ERAB Funding

Consolidation within the brewing sector has continued. Ever larger international brewing companies had their own research priorities and in-house expertise. They had developed well-established programmes to promote responsible consumption and they engaged in sector-wide funding of alcohol education charities. In these circumstances, collaborative research into the effects of alcohol on health was becoming less relevant to many of the participating companies. The Australian and New Zealand Medical Advisory Group was closed in 2005 and brewers funding for the ABMRF / The Foundation for Alcohol Research was terminated in 2015.

Over recent years, brewers have made technological strides in developing a new generation of high-quality alcohol-free and ultra-low alcohol beers to satisfy consumer demand for such products. It is becoming clear that this growing trend will have a significant impact on responsible social drinking both now and in the future.

In taking the difficult decision to end ERAB funding, The Brewers of Europe are proud of the legacy that has been created. Initially, it was intended to provide funding for a three-year period. In practice, this was extended to seventeen years. Key statistics can be found in Annex 5. The considerable investment of research money over that period has left a large body of ground-breaking publications in the scientific literature, and has seeded many lines of research that may otherwise not have been explored. The research summary which follows lists the 317 publications which have resulted from ERAB funded research. Annex 6 gives details of the high quality of these publications, 50% of which achieved an impact factor/score of over 4 (2021).

Although the current source of funding will no longer be available, many fruitful areas for future research have been identified. It is hoped that these will provide a sound basis for research applications to other funders particularly by the talented young scientists that have been nurtured through this unique collaboration.

ERAB Legacy

The long-term sponsorship by brewers of independent medical research has been a clear demonstration of the social responsibility that they have historically shown in many areas of endeavour.

Thanks to support by the Brewers of Europe, ERAB has been able to fund innovative, high-quality research on alcohol and health throughout Europe.

ERAB research outputs have profoundly improved our knowledge about the effects of alcohol on cardiovascular disease, cancer, liver disease, genetics of alcoholism, binge drinking and the personality types involved in underage drinking.

This knowledge has pointed the way to delivering interventions to significantly reduce harms, improve public health and recognise the benefits of social drinking.

The research programme has helped significantly in assessing the delicate balance between the harms associated with alcohol abuse and the potential benefits of moderate consumption.

It is apparent that a number of new researchers in this field would not have received funding for their work if it were not for ERAB. In a period during which research funding had been dramatically cut worldwide and researchers experienced difficulties in obtaining funds, ERAB was one of the few, if not the only, European funding agency that continued to provide support for alcohol research.

Many grantees have subsequently reported that the 'seedcorn' funding they received through ERAB had facilitated research work that then attracted major grant funding from other sources.

ERAB became a beacon to attract new scientific talent and to provide the opportunity to explore novel areas of research, to facilitate proof-of-concept, the development of more substantial projects and to open the way for further funding opportunities.

ERAB has encouraged joint working between large numbers of individuals and fostered future collaborations in public and private sectors.

Undoubtedly, many of these young researchers will go on to shape future large-scale research programmes and influence public health strategies across Europe.

Dr. David Long and Janet Witheridge
ERAB: The European Foundation for Alcohol Research,
www.erab.org

Summaries of ERAB Funded Research 2003 - 2022

Role of different types of alcohol on the risk of cancer: analysis of data from case-control studies conducted in Italy, Greece and Switzerland over the last two decades (2003) (EA 03 05)

Gallus S, Laboratory of Lifestyle Epidemiology, Instituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy

This research quantified the role of various aspects of alcohol consumption and particularly of type of alcoholic beverages, on the risk of several common cancers and cardiovascular diseases in Southern Europe, based on case-control studies.
Regarding cancer there was no association between cutaneous malignant melanoma and alcohol consumption. Alcohol consumption showed no consistent association with prostate cancer risk, but a significant inverse trend in risk for benign prostatic hyperplasia. For oral and pharyngeal cancer, the risk increased with 3-4 drinks/day or more. For laryngeal cancer the risk increased with 5-7 drinks/day or more. For upper aero-digestive tract cancers, for similar levels of ethanol consumption, the risk for drinkers of beer and spirits appeared to be comparable or lower to those of wine drinkers. This study suggests that the most prevalent alcoholic beverage in the country tends to be associated with the highest risk for cancer. The apparent discrepancy between health outcomes of alcohol consumption can be explained in terms of different patterns of drinking, and variable (baseline) characteristics of heavy drinkers in various populations.
Regarding cardiovascular diseases, alcohol drinking during meals was inversely related with risk of acute myocardial infarction (MI), whereas alcohol outside meals only was unrelated to the risk. Even after stopping drinking, the protection of alcohol drinking against MI may partly persist for several years.

Publications

Garavello W, Bosetti C, **Gallus S**, Dal Maso L, Negri E, Franceschi S and La Vecchia C (2006) Type of alcoholic beverage and the risk of laryngeal cancer. *European Journal of Cancer Prevention*, 15:69-73

Randi G, Altieri A, **Gallus S**, Franceschi S, Negri E, Talamini R and La Vecchia C (2005) History of cirrhosis and risk of digestive tract neoplasms. *Annals of Oncology*, 16:1551-1555

Altieri A, Garavello W, Bosetti C, **Gallus S** and La Vecchia C (2005) Alcohol consumption and risk of laryngeal cancer. *Oral Oncology*, 41:956-965

Negri E, La Vecchia C, Pelucchi C and Tavani A (2005) The risk of acute myocardial infarction after stopping drinking. *Preventive Medicine*, 40:725-728. (S. Gallus team)

Altieri A, Bosetti C, **Gallus S**, Franceschi S, Dal Maso L, Talamini R, Levi F, Negri E, Rodriguez T and La Vecchia C (2004) Wine, beer and spirits and risk of oral and pharyngeal cancer: a case-control study from Italy and Switzerland. *Oral Oncology*, 40:904-909

Augustin LSA, **Gallus S**, Tavani A, Bosetti C, Negri E and La Vecchia C (2004) Alcohol consumption and acute myocardial infarction: a benefit of alcohol consumed with meals? *Epidemiology*, 15(6):767-769

Crispo A, Talamini R, **Gallus S**, Negri E, Gallo A, Bosetti C, La Vecchia C, Dal Maso L, and Montella M (2004) Alcohol and the risk of prostate cancer and benign prostatic hyperplasia. *Urology*, 64:717-722. https://pubmed.ncbi.nlm.nih.gov/15491708/

Naldi L, **Gallus S**, Tavani A, Imberti GL and La Vecchia C (2004) Risk of melanoma and vitamin A, coffee and alcohol: a case-control study from Italy. *European Journal of Cancer Prevention*, 13:503-508

Theses and Awards

Dr. Gallus - ERAB Publications Award 2012

Alcohol, inflammation and atherosclerosis (2003) (EA 03 06)

Imhof A, Department of Internal Medicine, University of Ulm, Ulm, Germany

Moderate alcohol consumption is associated with reduced cardiovascular mortality compared to non-consumption of alcohol and heavy drinking. In a randomized controlled trial, the effect of consumption of moderate amounts of alcoholic and non-alcoholic beverages on monocyte migration, a crucial step in atherogenesis, was assessed. This short-term intervention showed that moderate amounts of alcohol inhibit monocyte migration.

In the same study moderate amounts of ethanol-containing beverages increased adiponectin concentrations, but sex-specific effects might depend on type of beverage consumed. Adiponectin might represent an important link between insulin resistance, type 2 diabetes, and atherosclerosis. Adiponectin improves insulin sensitivity and has several anti-inflammatory properties, and high concentrations of adiponectin were associated with lower risk of type 2 diabetes and future cardiovascular events.

These findings might represent mechanisms by which alcoholic beverages lower cardiovascular disease risk.

Publications

Kächele M, Wolff S, Kratzer W, Haenle M, Homann J, Trischler G, Koenig W and **Imhof A** (2015) Presence of fatty liver and the relationship between alcohol consumption and markers of inflammation. *Mediators of inflammation*, 278785

Imhof A, Plamper I, Maier S, Trischler G and Koenig W (2009) Effect of drinking on adiponectin in healthy men and women. *Diabetes Care*, 32:1101-1103

Imhof A, Blagieva R, Marx N and Koenig W (2008) Drinking modulates monocyte migration in healthy subjects: a randomised intervention study of water, ethanol, red wine and beer with or without alcohol. *Diabetes and Vascular Disease Research*, 5:48-53

Theses and Awards

Dr. Armin Imhof MD: Thesis for associate professorship ("Habilitation" in Germany); Rosa Blagieva MD, Stefan Wolff MD, Katrin Meitinger MD, Ines Plamper MD, Steffen Meier MD: Thesis for Medical Doctoral grade.

Alcohol consumption and risk of genetic alterations in genes involved in colorectal cancer in the Cohort Study on Diet and Cancer (2003) (EA 03 07)

Weijenberg MP, Departments of Epidemiology and Pathology, University of Maastricht, Maastricht, The Netherlands

In this project, the associations between consumption of alcohol and risk of colorectal cancer (CRC) were investigated in the prospective Netherlands Cohort Study on diet and cancer. This study included over 120 000 men and women with baseline information of total and beverage-specific alcohol consumption, including retrospective information on alcohol consumption five years prior to baseline. After 7.3 years of follow-up, it was concluded that a daily high consumption of alcohol of 30 grams or more, compared to abstaining, is associated with an increased risk of colorectal cancer in both men and women. The data suggest that the association is mainly explained by the alcohol content of alcoholic beverages, rather than other constituents. The association with alcohol appeared to be slightly stronger for more distal than proximal tumours, but there was no differential association for different molecular endpoints depending on markers for microsatellite instability and/or chromosomal instability. Specifically, beer consumption was also not significantly associated with colorectal tumours harbouring G>A mutations in the *KRAS* gene, as was hypothesized due to potential past contamination of beer with relatively large amounts of N-nitrosodimethylamine (NDMA). Both

alcohol dehydrogenase 1C (ADH1C) genotype and alcohol consumption were independently associated with an increased risk of CRC. However, there was no apparent evidence for modification of the association of alcohol consumption with CRC through the ADH1C genotype. Nevertheless, the interaction deserves further investigation in larger genetic epidemiologic studies.

Publications

Bongaerts BW, de Goeij AF, Wouters KA, van Engeland M, Gottschalk RW, Van Schooten FJ, Goldbohm RA, van den Brandt PA and **Weijenberg, MP** (2011) Alcohol consumption, alcohol dehydrogenase 1C (ADH1C) genotype, and risk of colorectal cancer in the Netherlands Cohort Study on diet and cancer. *Alcohol*, *45*(3), 217-225

Bongaerts BWC, van den Brandt PA, Goldbohm RA, de Goeij AFPM and **Weijenberg MP** (2008) Alcohol consumption, type of alcoholic beverage and risk of colorectal cancer at specific subsites. *International Journal of Cancer*, 123(10): 2411-2417

Bongaerts BWC, de Goeij AFPM, de Vogel S, van den Brandt PA, Goldbohm RA and **Weijenberg MP** (2007) Alcohol consumption and distinct molecular pathways to colorectal cancer. *British Journal of Nutrition*, 97(3): 430-434

Bongaerts BWC, de Goeij AFPM, van den Brandt P and **Weijenberg MP** (2006) Alcohol and the risk of colon and rectal cancer with mutations in the K-ras gene. *Alcohol,* 38(3): 147-154

Theses and Awards

Dr. Brenda Bongaerts - PhD 2008 Alcohol consumption as a risk factor for colorectal cancer. An epidemiological study on genetic susceptibility and molecular endpoints: Datawyse, Universiteit Pers Maastricht. ERAB Travel Award 2007.

Neuropsychobiological mechanisms underlying the co-dependence alcohol-nicotine and the respective neurotoxicities occurring during their combined consumptions and their withdrawals (2003) (EA 03 12)

De Witte P, Laboratory of Behavioural Biology, Université Catholique de Louvain, Louvain-la-Neuve, Belgium

In this study the action of nicotine on a specific part of the brain was investigated by microdialysis in rats. In addition, the release of specific amino acids in the

withdrawal stage following a 4-week period of nicotine and alcohol administration was studied.

The findings showed that small doses of nicotine may have a modulating effect on symptoms during the initial stages of ethanol withdrawal. The imbalance occurring between excitatory and inhibitory amino acids during withdrawal of alcohol after long-term exposure and during acute nicotine administration may be responsible for additional problems.

This research is of relevance to the treatment of alcoholics. It will help scientists to understand alcohol withdrawal symptoms and how they are affected by co-dependency with other drugs such as nicotine.

Publications

Lallemand F, Ward RJ, **De Witte P** and Verbanck P (2011). Binge drinking +/- chronic nicotine administration alters extracellular glutamate and arginine levels in the nucleus accumbens of adult male and female Wistar rats. *Alcohol and Alcoholism*, 46(4):373-382

D'Souza El-Guindy NB, Kovacs EJ and **De Witte P**, Spies C, Littleton JM, de Villiers WJS, Lott AJ, Plackett TP, Lanzke N, Meadows GG (2010). Laboratory models available to study alcohol-induced organ damage and immune variations: choosing the appropriate model. *Alcoholism: Clinical and Experimental Research*, 34(9):1489-1511

Lallemand F, Ward RJ and **De Witte P** (2007). Nicotine increases ethanol preference but decreases locomotor activity during the initial stages of chronic ethanol withdrawal. *Alcohol and Alcoholism*, 42(3):207-218

Lallemand F, Ward RJ, Dravolina O and **De Witte P** (2006). Nicotine-induced changes of glutamate and arginine in naïve and chronically alcoholized rats: an in vivo microdialysis study. *Brain Research*, 1111:48-60

Kashkin V and **De Witte P** (2005). Nicotine increases microdialysate brain amino acid concentrations and induces conditioned place preference. *European Neuro-Psychopharmacology*, 15:625-632

Theses and Awards

Dr. Dahchour - "Ethanol effects on Neuro-excitatory and neuroinhibitory Amino Acids in Rats: Brain Microdialysis Study".

Professor De Witte - ERAB Publications Award 2013.

Genetic and environmental influences on risk factors of adolescent alcohol use and problem use (2003) (EA 03 13)

van den Bree MBM, Cardiff University, UK

This study aimed at providing information into why some children show no signs of alcohol related problems while the lives of others are seriously harmed by the development of alcohol use and abuse. The focus of this twin study using questionnaires was the aetiology of substance use and misuse in adolescence and early adulthood.

The initiation of alcohol use appeared to be more strongly influenced by environmental factors such as parental attitudes, school policy on substance use and the local neighbourhood. Progression to more frequent use of alcohol was more strongly influenced by genetic factors. Peer substance use is not only an environmental risk factor, as the genes that increase adolescents' risk of heavy and problem alcohol use, are also, to some extent, the same genes that lead them to affiliate with peer groups that regularly use alcohol.

These findings have implications for intervention programmes and policy development by highlighting the role of environmental factors that may account for adolescent alcohol use while also underscoring the need to further understand the interplay between an adolescents' alcohol use and their likelihood of associating with an alcohol-using friendship group.

Publications

Glaser B, Shelton KH and **van den Bree MBM** (2010). The moderating role of close friends in the relationship between conduct problems and adolescent substance use. *Journal of Adolescent Health*, 47(1):35-42

Fowler T, Shelton K, Lifford K, Rice F, McBride A, Nikolov I, Neale MC, Harold G, Thapar A and **van de Bree MBM** (2007). Genetic and environmental influences on the relationship between peer alcohol use and own alcohol use in adolescents. *Addiction*, 102:894-903

Fowler T, Lifford K, Shelton K, Rice F, Thapar A, Neale MC, McBride A and **van den Bree MBM** (2007). Exploring the relationship between genetic and environmental influences on initiation and progression of substance use. *Addiction*, 101(3):413-422

Theses and Awards

The project has led to four PhD projects.

Dr. Fowler won an ERAB Young Investigator Award for work presented at the Conference of the European Society for Biomedical Research on Alcoholism (ESBRA) in Canterbury, September 2005.

Dr. Shelton won a Behaviour Genetics Travel award enabling her to present work at the Behaviour Genetics conference in Los Angeles in July, 2005.

Professor van den Bree - ERAB Publications Award 2013.

A comprehensive identification and characterisation of genes that are differentially expressed during the development and progression of alcohol induced liver disease (2003) (EA 03 15)

Reeves HL, The Liver Group, Newcastle University, Newcastle upon Tyne, UK

Although non-alcoholic fatty liver disease (NAFLD) is increasingly common, only a minority of affected individuals develop fibrotic liver disease. The reasons for these differences in individual susceptibility to progressive disease are unclear, but family/ethnic studies suggest that genetic factors play a significant role.

This study found a functional polymorphism in the *KLF6* gene associated with advanced NAFLD. Further study of *KLF6* may enhance understanding of this disease process.

Publications

Miele L, Beale G, Patman G, Nobili V, Leathart J, Grieco A, Abate M, Friedman SL, Narla G, Bugianesi E, Day CP and **Reeves HL** (2008) The Kruppel like factor 6 genotype is associated with fibrosis in non-alcoholic fatty liver disease. *Gastroenterology*, 135(1):282-291

Theses and Awards

Dr. Kendrick - PhD

Development of a rodent model of beer consumption: investigation on the differential contribution of gustatory and pharmacological factors to beer drinking behaviour (2004) (EA 04 01)

Colombo G, Neuroscience Institute, National Research Council of Italy, Cagliari, Italy

This study evaluated the effect of an environmental manipulation being a prolonged exposure to non-alcoholic beer with increasing concentrations of alcohol on the genetically determined predisposition and avoidance to consume alcohol of Sardinian alcohol-preferring (sP) and Sardinian alcohol-non preferring (sNP) rats, respectively. It was predicted that long-term exposure to a highly palatable beverage, made of non-alcoholic beer plus alcohol, would have permanently (a) increased – to "unusually" high levels – alcohol consumption in sP rats, and (b) overcome the inherent reluctance of sNP rats to consume alcohol. Both results would have been interpreted as the demonstration of the development of "psychological" dependence on alcohol.

However, the results of the study unequivocally demonstrated that, in both rat lines, (a) beer drinking was mostly driven by the gustatory aspects of beer, and (b) this long-term exposure to alcoholic beer did not produce any permanent, "unusually" high intake of alcohol once the beer taste was removed.

Publications

Lobina C, Carai MAM, Froestl W, Mugnaini C, Pasquini S, Corelli F, Gessa GL and **Colombo G** (2011) Activation of the $GABA_B$ receptor prevents nicotine-induced locomotor stimulation in mice. *Frontiers in Psychiatry*, 2:76

Maccioni P, Thomas AW, Carai MAM, Gessa GL, Malherbe P and **Colombo G** (2010) The positive allosteric modulator of the GABA (B) receptor, *rac*-BHFF, suppresses alcohol self-administration. *Drug and Alcohol Dependence*, 109:96-103

Orrù A. Lobina C, Maccioni P, Gessa G.L., Carai MAM and **Colombo G.** (2007) Repeated exposure to alcoholic beer does not induce long-lasting changes in alcohol self-administration and intake in Sardinian alcohol-preferring and Sardinian non-preferring rats. *Alcohol and Alcoholism*, 42(6):513-524

Maccioni P, Orrù A, Korkosz A, Gessa GL, Carai MAM and **Colombo G** and Bienkowski P (2007) Cue-induced reinstatement of ethanol seeking in Sardinian alcohol-preferring rats. *Alcohol*, 41:31-39

Challenging alcohol-related aggression expectancies (2004) (EA 04 02)

McMurran M, University of Nottingham, UK

Expectancies may be one target in interventions to reduce alcohol-related aggression. In a study with male students, participants were asked to recall both alcohol-related aggressive and alcohol-related non-aggressive events. Both seem to have the potential to increase alcohol-aggression outcome expectancies. This may elevate the risk for alcohol-related aggression, at least temporarily.
In treatment for alcohol-related aggression, asking clients to recount incidents where they were aggressive or violent after drinking may temporarily increase their risk by increasing alcohol-aggression outcome expectancies. This needs to be taken into account by advising those in treatment to avoid risky situations. In this study it was hypothesized that recounting incidents where drinking did not lead to violence would lead to a reduction in alcohol-aggression expectancies, and hence reduce risk. This was not the case, and indeed alcohol-aggression expectancies were elevated in this condition. Therefore, indications are that this is not a useful therapeutic strategy for risk reduction. It is important that therapists are aware of this. Effective ways of challenging alcohol-related aggression expectancies remain to be identified.

Publications

McMurran M and McCulloch, A (2009) Alcohol-aggression outcome expectancies and their responsiveness to event recall. *Addiction Research and Theory*, 17(1):54-63

McMurran M (2009). The relationships between alcohol use, trait aggression and the alcohol-aggression outcome expectancy in male students. *Journal of Substance Use*, 14(1):1-9

Mechanisms of the protective effects of alcohol consumption on cardiovascular risk and on myocardial preconditioning (2004) (EA 04 07)

Crea F, Institute of Cardiology, Catholic University of the Sacred Heart, Rome, Italy

The aim of this research project was to investigate potential biological mechanisms explaining the association between moderate alcohol consumption and lower cardiovascular risk observed in several previous studies. These mechanisms were investigated in healthy subjects and in patients with coronary artery disease.
First of all, the problem of confounding that has been raised as a radical critique to observational studies on alcohol and health appears to be of minor concern. Abstainers and moderate drinkers from the Moli-sani cohort were comparable in the majority of aspects, only socio- economic status appearing as a possible true confounder. Taken together, these results show that moderate alcohol consumption has a remarkably positive effect on risk profile for cardiovascular diseases.
In contrast, heavy alcohol consumption increases the risk of cardiovascular events through a variety of mechanisms including activation of inflammatory cells, hypertension and abolition of ischemic preconditioning. The latter, in particular, is likely to play a key role in explaining the higher mortality following an acute myocardial infarction observed in heavy and binge drinkers.

Publications

Marinaccio L, Lanza GA, Niccoli G, Fabretti A, Lamendola P, Barone L, Di Monaco A, Di Clemente F and **Crea F**. (2008) Effect of low doses of alcohol on the warm-up phenomenon in patients with stable angina pectoris. *American Journal of Cardiology*, 102(2):146-149

Niccoli G, Altamura L, Fabretti A, Lanza GA, Biasucci LM, Rebuzzi AG, Maria Leone A, Porto I, Burzotta F, Trani C and **Crea F** (2008) Ethanol abolishes ischemic preconditioning in humans. *Journal of the American College of Cardiology*, 51(3):271-275

Di Castelnuovo A, Costanzo S, Donati MB, Lacoviello L and de Gaetano G (2007) Alcohol consumption and cardiovascular risk: an epidemiological perspective. *Nutrition, Metabolism and Cardiovascular diseases*, 17:561-564

Theses and Awards

Dr. Leone - PhD

The e-UNICAL project: A feasibility and effectiveness study into delivering an electronic feedback and social norms intervention designed to decrease university students' *consumption of alcohol* (2005) (EA 05 08)

Bewick BM, Division of Psychological and Social Medicine, School of Medicine, Faculty of Medicine and Health, University of Leeds, Leeds, UK

The e-UNICAL project investigated the feasibility and effectiveness of delivering a web-based social norms and personalised feedback intervention for alcohol use to university students. It also investigated the relationship between alcohol consumption, associated risk behaviours and mental health.

Intervention participants significantly reduced their units of alcohol per occasion from pre-survey levels. This reduction was maintained at follow-up. There was no significant change within control participants. Intervention participants rated the intervention favourably and in general there was no difference in ratings between low, moderate and high-level drinkers. The relative risk of experiencing negative consequences/engaging in risky behaviour was higher in students who consumed alcohol at moderate or high levels in comparison to their low-level peers.

These results suggest that a personalised feedback and social norms intervention can be effective in reducing alcohol consumption amongst the UK student population. In light of these findings, it is suggested that within the student population web-based social norms and personalised feedback interventions should be more widely available. While the findings are positive further research is needed to understand the mechanisms of change and how the impact of the intervention could be improved.

Publications

Marley, S, Bekker HL and **Bewick BM** (2016) Responding to personalized social norms feedback from a web-based alcohol reduction intervention for students: Analysis of think-aloud verbal protocols. *Psychology and Health*, 31(9): 1007-1024

Bewick BM, West RM, Barkham M, Mulher, B, Marlow R, Traviss G and Hill AJ (2013) The effectiveness of a web-based personalized feedback and social norms alcohol intervention on United Kingdom university students: Randomized controlled trial. *Journal of Medical Internet Research*, 15(7): e137

Bewick BM, West RM, Gill J, O'May F, Mulhern B, Barkham M and Hill AJ (2010) Providing web-based feedback and social norms information to reduce student alcohol intake: A multi-site investigation. *Journal of Medical Internet Research*, 12(5): e59

Cunningham JA, Khadjesari Z, **Bewick BM** and Riper H (2010) Internet-based interventions for problem drinkers: from efficacy trials to implementation. *Drug and Alcohol Review*, 29(6): 617–622

Bewick BM, Mulhern B, Barkham M, Trusler K, Hill AJ and Stiles WB (2008) Changes in undergraduate student alcohol consumption as they progress through university. *BMC Public Health*, 8:163

Theses and Awards

Dr. Bridgette Bewick - PhD 2010 - Measuring, monitoring and modifying students' mental health, ERAB Publications Award 2016.

Identification of a candidate gene influencing alcohol intake, using a mouse line with alcohol preference induced by ENU mutagenesis (2005) (EA 05 09)

Thomas HC, Department of Medicine Imperial College, St Mary's Hospital – UK

This study provided a new and important link between a specific gene and increased alcohol consumption that could underlie some forms of alcohol abuse.

The first ENU induced model of alcoholism (alco-22) has now been mapped demonstrating that the mutation resulting in increased alcohol intake is in the gene encoding the GABA-A B1 subunit. This project was funded to allow mapping of the mutation in a second mouse line (alco-2) to determine whether a second gene might be involved.

The results from this study have narrowed down the candidate region for high ethanol preference in the ALCO/2 mouse line to 10 Mb at the telomeric end of chromosome 11. This region includes interesting candidate genes like Sstr2 and Grin2c, and the QTL's for alcohol preference Alcp 18 (male specific) and 20 (female specific).

Further funding would be needed to support the ongoing breeding, genotyping and phenotyping efforts of the offspring of the ALCO/2 line, including three possibly informative recombinants.

Publications

Anstee QM, Knapp S, Maguire EP, Hosie AM, Thomas P, Mortensen M, Bhome R, Martinez A, Walker SE, Dixon CI, Ruparelia K, Montagnese S, Kuo YT, Herlihy A, Bell JD, Robinson I, Guerrini I, McQuillin A, Fisher EMC, Ungless MA, Gurling JMD, Morgan MY, Brown SDM, Stephens DN, Belelli D, Lambert JJ, Smart TG and **Thomas HC** (2013) Mutations in the *Gabrb*1 gene promote alcohol consumption through increased tonic inhibition. *Nature Communications,* 4(2816)

Investigations on glutamatergic and GABAergic disturbances that may result in fetal alcohol syndrome (2005) (EA 05 12)

Zink M, Departments of Psychiatry Psychopharmacology, Central Institute of Mental Health, Mannheim, Germany

Fetal alcohol syndrome (FAS) can cause mental retardation. However, the molecular details of the detrimental influences exerted by ethanol have not been clear until now. This research established an animal model and was able to reproduce in rats a variety of core-features of FAS- children. The last trimenon of human pregnancy was defined as the most critical period with regard to the learning disabilities. Alterations in gene expression were observed. Because the functions of these genes are well described, the results contribute to an improved understanding of the pathogenesis of FAS and might lead to the development of new procedures in prophylaxis and treatment.

Publications

Zink M, Ferbert T, Franck ST, Seufert P, Gebicke-Haeter PJ and Spanagel R (2011) Perinatal exposure to alcohol disturbs spatial learning and glutamate transmission-related gene expression in the adult hippocampus. *European Journal of Neuroscience*, 34:457-468

Spanagel R (2009) Alcoholism: a systems approach from molecular physiology to addictive behavior. *Physiological Reviews*, 89:649-705

Zink M, Araç G, Frank STh, Gass P, Gebicke-Härter PJ and Spanagel R (2009) Perinatal exposure to alcohol reduces the expression of complexins I and II. *Neurotoxicology and Teratology*, 31:400-405

Alcohol-induced neurogenesis: Functional characterization of increased formation of nerve cells in hippocampus in response to moderate voluntary ethanol intake (2005) (EA 05 18)

Brené S, Department of Neurotec division of Psychiatry, Karolinska University Hospital, Stockholm, Sweden

This study analysed hippocampal neurogenesis in the two-bottle free-choice model of alcohol consumption in single housed rats and mice. The results showed that depending on circumstances alcohol consumption can increase, decrease or have no effect on hippocampal neurogenesis (the process by which neurons, are produced by neural stem cells). Most likely what determines which effect voluntary alcohol consumption has on hippocampal neurogenesis is whether there is a stress component involved in overall consumption behavior.
Overall, it appears that alcohol consumption has the potential to alter the rate of formation of new nerve cells. Thus, the long- term effects of alcohol on brain function can in part be mediated via modulation of the rate of formation of new nerve cells.

Publications

Åberg E, Perlmann T, Olson L and **Brené S** (2008) Running increases neurogenesis without retinoic acid receptor activation in the adult dentate gyrus. *Hippocampus*, 18(8):785-792. https://doi.org/10.1002/hipo.20438

Effect of ethanol drinking on the metabolism of essential fatty acids in 3 very different European populations (2005) (EA 05 20)

De Lorgeril M, Laboratoire Nutrition, Vieillissement et Maladies Cardiovasculaires (NVMCV), Université Joseph Fourier, La Tronche, France

The main aim of this study was to investigate the effects of moderate ethanol drinking on the metabolism of the essential omega-3 fatty acids in humans. A secondary aim was

to investigate whether some genetic polymorphisms may play a role in that interaction. The data, obtained from quite a large sample of middle-aged men and women, confirm previous human and animal findings suggesting that moderate alcohol consumption results in increased omega-3 fatty acid levels in both the plasma and cell membranes.

This means that the effect of moderate alcohol drinking on the metabolism of omega-3 fatty acids could, at least partly, explain the protective effect of alcohol on the risk of cardiovascular diseases. This was a totally new finding regarding the role of moderate ethanol drinking in the context of cardiovascular diseases.

Publications

di Giuseppe R, **de Lorgeril M**, Salen P, Laporte F, Di Castelnuovo A, Krogh V, Siani A, Arnout J, Cappuccio FP, van Dongen M, Donati MB, de Gaetano G and Lacoviello L, on behalf of the European Collaborative Group of the IMMIDIET Project (2009) Alcohol consumption and n-3 polyunsatured fatty acids in healthy men and women from 3 European populations. *American Journal of Clinical Nutrition*, 89:354-362

Latella MC, Di Castelnuovo A, **de Lorgeril M**, Arnout J, Cappuccion FP, Krogh V, Siani A, van Dongen M, Donati MB, de Gaetano G and Lacoviello L, on behalf of the European Collaborative Group of the IMMIDIET project (2009) Genetic variation of alcohol dehydrogenase type 1C (ADH1C), alcohol consumption, and metabolic cardiovascular risk factors: results from the IMMIDIET group. *Atherosclerosis*, 207:284-290

Stress reactivity, psychopathology and age at first alcohol use (2006) (EA 06 09)

Huizink A, Department of Child and Adolescent Psychiatry, Erasmus Medical Centre, Rotterdam, The Netherlands

For the prevention of (heavy) alcohol use in youth, it is important to better describe, identify, and predict the complex nature and course of alcohol consumption and associated psychopathology. This research looked at the age of alcohol initiation among adolescents with either symptoms of antisocial behaviour (so-called externalizing problems) or symptoms of depression (so-called internalizing problems). The researchers used stress response tasks to measure the change in heart rate in these adolescents. This was used as a measure of autonomic functioning to see if it influenced the age of alcohol initiation. Results showed that there was no association between antisocial behaviour or depression symptoms and the age

of alcohol initiation. Greater heart rate reactivity however, might predict earlier initiation of alcohol use. This could mean that alcohol is used at an early age to lower stress instead of using it to raise arousal levels (as suggested by other studies). This research contributes to the identification of adolescents at risk for using alcohol at an early age and may provide insights for better health promotion interventions.

Publications

Evans BE, Greaves-Lord K, Euser AS, Franken IHA and **Huizink AC** (2012) The relation between hypothalamic–pituitary–adrenal (HPA) axis activity and age of onset of alcohol use. *Addiction*, 107(2):312-322

Greaves-Lord K, Tulen JHM, Dietrich A, Sondeijker FEPL, van Roon A, Oldehinkel AJ, Ormel J, Verhulst FC and **Huizink AC** (2010) Reduced autonomic flexibility as a predictor for future anxiety in girls from the general population: the TRAILS study. *Psychiatry Research*, 179(2):187-193

Van Oort FVA, Greaves-Lord K, Verhuslt FC, Ormel J and **Huizink AC** (2009) The developmental course of anxiety symptoms during adolescence: the TRAILS study. *Journal of Child Psychology and Psychiatry*, 50(10):1209-1217

Greaves-Lord K, **Huizink AC**, Oldehinkel AJ, Ormel J, Verhulst FC and Ferdinand RF (2009) Baseline cortisol measures and developmental pathways of anxiety in early adolescence. *Acta Psychiatrica Scandinavica*, 120(3):178-186

Huizink AC, Greaves-Lord K, Oldehinkel AJ, Ormel J and Verhuslt FC (2009) Hypothalamic-pituitary-adrenal axis and smoking and drinking onset among adolescents: the longitudinal cohort study TRAILS. *Addiction*, 104:1927-1936

Theses and Awards

Professor Dr. Huizink – ERAB Exchange Award 2006, ERAB Publications Award 2012
Dr. Brittany Evans - PhD 2013

A double-blind randomized controlled study on alcohol intake and craving reduction in alcohol-dependent patients comparing baclofen 10 mg, baclofen 20 mg and placebo (2006) (EA 06 19)

Leggio L, Institute of Internal Medicine and Department of Neuroscience, Catholic University of Rome, Rome, Italy

Baclofen is used as medication in alcohol dependent individuals to reduce alcohol intake and craving. Chronic alcohol abuse alters hormone levels and body composition.

The researchers investigated, in several longitudinal studies, the role of other hormones in alcohol dependent patients treated with Baclofen. Data suggest that specific hormones related to the hypothalamic-pituitary-thyroid axis (e.g. TSH and free T3) could be involved in the neurobiology of alcohol craving. An additional study, on the role of volume-regulating hormones, suggested that alcohol craving could be influenced by fluid volume intake. Another study showed that hormones of the hypothalamic-pituitary-adrenal axis can play a role in nutritional and metabolic parameters in alcoholics, for example changes in fat mass. Conversely, these hormones might also play a role in the nutritional recovery after a period of total abstinence. Finally, the researchers evaluated the association between affective and psychiatric disorders (e.g. anxiety) among alcoholics with craving and the effect of a period of abstinence.

The results suggested that Baclofen, which has anti-craving properties, could be helpful in ameliorating psychiatric features in alcohol dependent patients.

Publications

Aoun EG, Jimenez VA, Vendruscolo LF, Walter NAR, Barbier E, Ferrulli A, Haass-Koffler CL, Darakjian P, Lee MR, Addolorato G, Heilig M, Hitzemann R, Koob GF, Grant KA and **Leggio L** (2017) A relationship between the aldosterone–mineralocorticoid receptor pathway and alcohol drinking: preliminary translational findings across rats, monkeys and humans. *Molecular Psychiatry*, 23: 1466–1473)

Aoun EG, Lee MR, Haass-Koffler CL, Swift RM, Addolorato G, **Leggio L** (2015) Relationship between the thyroid axis and alcohol craving. *Alcohol and Alcoholism*, 50(1):24-29

Lugoboni F, Mirijello A, Faccini M, Casari R, Cossari A, Musi G, Bissoli G, Quaglio G, Addolorato G (2014) Quality of life in a cohort of high-dose benzodiazepine dependent patients. *Drug and Alcohol Dependence*, 142:105-109

Addolorato G, Mirijello A, **Leggio L**, Ferulli A, D'Angelo C, Vassallo G, Cossari A, Gasbarrini G, Landolfi R, Agres S, Gasbarrini A and Gemelli OLT Group (2013) Liver transplantation in alcoholic patients: impact of an alcohol addiction unit within a liver transplant center. *Alcoholism: Clinical and Experimental Research*, 37(9): 1601-1608

Leggio L, Ferrulli A, Zambon A, Caputo F, Kenna GA, Swift RM and Addolorato G (2012) Baclofen promotes alcohol abstinence in alcohol dependent cirrhotic patients with hepatitis C virus (HCV) infection. *Addictive Behaviors*, 37(4):561-564

Leggio L, Ferrulli A, Cardone S, Nesci A, Miceli A, Malandrino N, Capristo E, Canestrelli B, Monteleone P, Kenna GA, Swift RM and Addolorato G (2012) Ghrelin system in alcohol-dependent subjects: role of plasma ghrelin levels in alcohol drinking and craving. *Addiction Biology*, 17(2):452-464

Addolorato G, **Leggio L**, Ferrulli A, Cardone S, Bedogni G, Caputo F, Gasbarrini G, Landolfi R and the Baclofen Study Group (2011) Dose-response effect of baclofen in reducing daily alcohol intake in alcohol dependence: secondary analysis of a randomized, double-blind, placebo controlled trial. *Alcohol and Alcoholism*, 46(3):312-317

Leggio L, Kenna GA, Ferrulli A, Zywiak WH, Caputo F, Swift RM and Addolorato G (2011) Preliminary findings on the use of metadoxine for the treatment of alcohol dependence and the alcoholic liver disease. *Human Psychopharmacology: Clinical and Experimental*, 26(8):554-559

Montalto M, Gallo A, Ferrulli A, Visca D, Campobasso E, Cardone S, D'Onofrio F, Santoro L, Covino M, Mirijello A, **Leggio L**, Gasbarrini G and Addolorato G (2011) Fecal calprotectin concentrations in alcoholic patients: a longitudinal study. *European Journal of Gastro-Enterology and Hepatology*, 23(1): 76-80

Ferrulli A, **Leggio L**, Cardone S, D'Angelo C, Mirijello A, Vonghia L, Micli A, Gasbarrini G and Addolorato G (2010) Psychosocial findings in alcohol-dependent patients before and after three months of total alcohol abstinence. *Frontiers in Psychiatry*, 1:17

Leggio L (2010) Role of the ghrelin system in alcoholism: acting on the growth receptor to treat alcohol-related disorders. *Drug News & Perspectives* 23(3):157-166

Leggio L, Cardone S, Ferrulli A, Kenna G A, Diana M, Swift R M and Addolorato G (2010) Turning the clock ahead: potential preclinical and clinical neuropharmalogical targets for alcohol dependence. *Current Pharmaceutical Design*, 16(19):2159-2181

Addolorato G and **Leggio L** (2010) Safety and efficacy of Baclofen in the treatment of alcohol-dependent patients. *Current Pharmaceutical Design*, 16(19):2113-2117

Addolorato G, **Leggio L**, Cardone S, Ferrulli A and Gasbarrini G (2009) Role of the $GABA_B$ receptor system in alcoholism and stress: focus on clinical studies and treatment perspectives. *Alcohol*, 43(7) :559-563

Leggio L (2009) Understanding and treating alcohol craving and dependence: recent pharmacological and neuroendocrinogical findings – ESBRA-Nordmann 2008 Award Lecture. *Alcohol and Alcoholism*, 44(4):341-352

Leggio L, Malandrino N, Ferrulli A, Cardone S, Miceli A, Gasbarrini G, Capristo E and Addolorato G (2009) Is cortisol involved in the alcohol-related fat mass impairments? A longitudinal clinical study. *Alcohol and Alcoholism*, 44(2):211-215

Leggio L, Ferrulli A, Malandrino N, Miceli A, Capristo E, Gasbarrini G and Addolorato G (2008) Insulin but not insulin growth factor-1 correlates with craving in currently drinking alcohol-dependent patients. *Alcoholism: Clinical and Experimental Research*, 32(3):450-458

Leggio L, Ferrulli A, Cardone S, Malandrino N, Mirijello A, D'Angelo C, Vonghia L, Miceli A, Capristo E, Kenna GA, Gasbarrini G, Swift RM and Addolorato G. (2008) Relationship between the hypothalamic-pituitary-thyroid axis and alcohol craving in alcohol-dependent patients: a longitudinal study. *Alcoholism: Clinical and Experimental Research*, 32(12):2047-2053

Addolorato G, **Leggio L**, Ferrulli A, Cardone S, Vonghia L, Mirijello A, Abenavoli L, D'Agelo C, Caputo F, Zambon A, Haber PS and Gasbarrini G (2007) Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. *The Lancet*, 370:1915-1922

Theses and Awards

Dr. Leggio went on to gain additional clinical research experience and training at Brown University (Providence, RI) at the Center for Alcohol and Addiction Studies (CAAS). He is also the recipient of an ERAB Publications Award 2012, and ERAB Travel Awards 2006/7/12.

Delineating the role of TGF-β signal transduction in alcohol dependent steatosis and steatohepatitis (2006) (EA 06 24)

Dooley S, Department of Medicine II, University Hospital, Mannheim, Germany

Alcohol intake can induce liver damage. This research investigated how ethanol interacts with other molecules within liver cells. Experiments using isolated liver cells found that the transforming growth factor TGF-β, a cell signalling protein, regulates the expression of enzymes involved in alcohol metabolism. TGF-β contributes to alcohol induced liver damage by stimulating fatty liver and liver fibrosis processes. Both, ethanol and TGF-β are toxic to liver cells. A combination of the two, further enhances the effect and can lead to cell death.

In studies with mice having pre-existing liver damage, presence and signalling of TGF-β enhance the deleterious effect of alcohol intoxication compared to mice with undamaged livers.
The results need to be further delineated and then have the potential to develop better treatment strategies for patients with liver damage due to alcohol intoxication.

Publications

Meyer C, Meindl-Beinker NM and **Dooley S** (2010) TGF-beta signalling in alcohol induced hepatic injury. *Frontiers in Bioscience (Landmark Edition)*, 1(15) :740-9

Ciuclan L, Singer MV, Craciun C and **Dooley S** (2010) Negative feedback regulation of TGF-β signaling by the Ski oncoprotein in mouse hepatocytes. *Annals of RSCB*, 15(1):19-27

Ciuclan L, Ehnert S, Ilkavets I, Weng H-L, Gaitantzi H, Tsukamoto H, Ueberham E, Singer MV, Breitkopf K and **Dooley S** (2010) TGF-beta enhances alcohol dependent hepatocyte damage via down regulation of alcohol dehydrogenase I. *Journal of Hepatology*, 52(3):407-416

Seth D, D'Souza NB, Guindy EI, Apte M, Mari M, **Dooley S**, Neuman M, Haber PS, Kundu GC, Darwanto A, de Villiers WJ, Vonlaufen A, Xu Z, Phillips P, Yang S, Goldstein D, Pirola RM, Wilson JS, Moles A, Fernández A, Colell A, García-Ruiz C, Fernández-Checa JC, Meyer C and Meindl-Beinker NM (2010) Alcohol, Signaling and ECM turnover. Alcohol: *Clinical and Experimental Research*, 34(1) :4-18

Breitkopf K, Nagy LE, Beier JI, Mueller S, Weng H and **Dooley S** (2009) Current experimental perspectives on the clinical progression of Alcoholic Liver Disease (ALD). *Alcohol: Clinical and Experimental Research*, 33(10):1647-1655

Haas SL, Fitzner B, Jaster R, Wiercinska E, Gaitantzi H, Jesenowski R, Löhr JM, Singer MV, **Dooley S** and Breitkopf K (2009) Transforming growth factor-beta induces nerve growth factor expression in pancreatic stellate cells by activation of the ALK-5 pathway. *Growth Factors*, 27(5) :289-299

Dooley S, Hamzavi J, Ciuclan L, Gogoy P, Ilkavets I, Ehnerts S, Ueberham E, Gebhardt R, Kanzler S, Geier A, Breitkopf K, Weng H and Mertens PR (2008) Hepatocyte-specific Smad7 expression attenuates TGF-β mediated fibrogenesis and protects against liver damage. *Gastroenterology*, 135(2) :642-659

Meindl-Beinker NM and **Dooley S** (2008) TGF-β and hepatocyte trans-differentiation in liver fibrogenesis. *Journal of Gastroenterology and Hepatology*, 23(Suppl.1):122-127

Theses and Awards

Dr. Breitkopf - Thesis for associate professorship ("Habilitation" in Germany);
Dr. Loredana Ciuclan - PHD
Professor Dooley - ERAB Publications Award 2016

A follow-up study on determinants for early alcohol debut and consequences of early debut for later psychosocial well-being, lifestyle and health (2006) (EA 06 27)

Grønbæk M, The Danish National Institute of Public Health, Copenhagen, Denmark

This research aimed at identifying risk factors for adolescents' health and health behaviour. Firstly, the characteristics of participants of the Danish Youth Cohort were assessed and compared with non-participants, to identify any differences in these groups. A follow-up study focused on social inequality in drinking onset. Results showed that adolescents from the wealthiest families, especially boys, were most at risk of early drinking onset. No differences in early drinking onset were found among socio-economic groups among girls. Secondly, the effect of early drinking onset on binge drinking across socioeconomic groups was investigated. The researchers concluded that the causal effect of early drinking onset on binge drinking vary across socioeconomic groups among boys. This means that there is social differentiation in the consequences of early drinking onset and indicates that already in adolescence socially differential vulnerability to alcohol does exist.

Publications

Vinther-Larsen M, Riegels M, Rod MH, Schiotz M, Curtis T and **Grønbaek M** (2010) The Danish youth cohort: characteristics of participants and non-participants and determinants of attrition. *Scandinavian Journal of Public Health*, 38:648-656

Eliasen M, Kjær SK, Munk C, Nygård M, Sparén P, Tryggvadottir L, Liaw KL and **Grønbæk M** (2009) The relationship between age at drinking onset and subsequent binge drinking among women. *European Journal of Public Health*, 19 (4): 378–382 (ERAB funding not acknowledged)

The effect of ethanol on Histone Acetylation at Pro-Inflammatory Cytokine Genes and its contribution to the clinical syndrome of Alcoholic Hepatitis (2006) (EA 06 39)

Jones DEJ, School of Clinical Medical Sciences, University of Newcastle upon Tyne, UK

Acute alcoholic hepatitis is characterized by a disproportionate inflammation response in the liver. Using cell studies, this research investigated the role of ethanol in cell signalling and gene regulation related to alcoholic hepatitis. Results showed that the association between ethanol, acetate (a breakdown product of ethanol), histone acetylation (essential in gene regulation) and the expression of cell signalling molecule (i.e. cytokines) reveals a possible therapeutic target for acute alcoholic hepatitis. Additionally, the importance of acetyl-coA (a key molecule in cellular processes) reinforces the intimate relationship between metabolism and immunity and the role of the liver as intersection of these vital processes. Moreover, the development of inhibitors of certain enzymes may allow modulation of inflammation in acute alcoholic hepatitis without affecting normal energy generation and storage pathways.

Publications

Kendrick SFW, O'Boyle G, Mann J, Zeybel M, Palmer J, **Jones DEJ** and Day CP (2010) Acetate, the key modulator of inflammatory responses in acute alcoholic hepatitis. *Hepatology*, 51:1988-1997

Generation and characterization of human monoclonal single chain antibodies specific to phosphatidylethanol (2006) (EA 06 40)

Savolainen M, Department of Internal Medicine, University of Oulu, Oulu, Finland

Phosphatidylethanols (PEth) are a group of alcohol-modified phospholipids present in cell membranes after heavy drinking. This research showed, for the first time, that antibodies against PEth can be produced with recombinant DNA techniques.

Recombinant techniques will provide means to effectively select new monoclonal antibodies that are smaller in size and with higher binding affinity to be used for PEth-specific immunoassays.
These antibodies contain protein sequence tags that will help use these antibodies in various ways for PEth analysis and detection. The recombinant antibodies could also be produced in large-scale production facilities for commercial purposes.

Publications

Nissinen AE, Laitinen LM, Kakko S, Helander A, **Savolainen MJ** and Hörkkö S (2012) Low plasma antibodies specific for phosphatidylethanol in alcohol abusers and patients with alcoholic pancreatitis. *Addiction Biology*, 17(6):1057-1067

Theses and Awards

Dr. Antti Nissinen - PhD 2011 Humoral immune response to phosphatidylethanol. Acta Universitatis Ouluensis D 1113. http://urn.fi/urn:isbn:9789514295232

Identification of inflammatory and angiogenic signaling mechanisms modulated by beer and red wine polyphenols (2006) (EA 06 41)

Soares R, Department of Biochemistry, University of Porto, Porto, Portugal

Angiogenesis (the formation of new blood vessels) and inflammation occur in diseases such as cancer and atherosclerosis. This research aimed at identifying whether polyphenols present in beer and red wine affect the molecular mechanisms of these processes. Results of cell and rat studies demonstrated that specific polyphenols found in beer (xanthohumol and isoxanthohumol) can be used as anti-inflammatory and anti-angiogenic agents. Another polyphenol (8-prenylnaringenin), manifested pro-angiogenic action which might be relevant for pathological conditions exhibiting angiogenic impairment.

Publications

Negrão R, Costa R, Duarte D, Gomes TT, Coelho P, Guimaraes JT, Guardão L, Azevedo I and **Soares R** (2012) Xanthohumol-supplemented beer modulates angiogenesis and inflammation in a skin wound healing model. Involvement of local adipocytes. *Journal of Cellular Biochemistry*, 113(1), 100-109

Negrão R, Costa R, Duarte D, Taveira Gomes T, Mendanha M, Moura L, Vasques L, Azevedo I and **Soares R** (2010) Angiogenesis and inflammation signaling are targets of beer polyphenols on vascular cells. *Journal of Cellular Biochemistry*, 111(5) :1270-1279

Costa R, Carneiro A, Rocha A, Pirraco A, Falcao M, Vasques L and **Soares R** (2009) Bevacizumab and ranibizumab on microvascular endothelial cells: a comparative study. *Journal of Cellular Biochemistry*, 108(6) :1410-1417

Lopes FCM, Rocha A, Pirraco A, Regasini LO, Silva DHS, Bolzani VS, Azevedo I, Carlos IZ and **Soares R** (2009) Anti-angiogenic effects of pterogynidine alkaloid isolated from Alchornea glandulosa. *BMC Complementary Medicine and Therapies*, 9:15

Theses and Awards

Dr. Flavia Lopes - PhD 2008
Dr. Rita Negrão - PhD 2012
Dr. Susana Guerreiro - PhD 2012
Dr. Renata Ramalho - PhD 2013
Ms. Raquel Costa - Masters 2011

The impact of methionine metabolism for the incidence and the clinical course of alcohol-dependency (2007) (EA 07 04)

Linnebank M, Dept. Neurology, Hagen-Ambrock and University of Witten/Herdecke, Germany

Various studies have shown that plasma homocysteine (HCY) serum levels are elevated in actively drinking alcohol-dependent patients and during alcohol withdrawal, while rapidly declining during abstinence. Hyperhomocysteinemia has been associated not only with blood alcohol concentration (BAC), but also with deficiency of different B-vitamins, particularly folate, pyridoxine and cobalamin. This study included 168 inpatients (110 men, 58 women) after admission for detoxification treatment. BAC, folate, cobalamin, pyridoxine, thiamine and riboflavin were obtained on admission (Day 1). HCY was assessed on Days 1, 7 and 11. HCY levels significantly declined during withdrawal. General linear models and linear regression analysis showed an influence of BAC, folate and riboflavin on the HCY levels on admission as well as on HCY changes occurring during alcohol withdrawal. No significant influence was found for thiamine, cobalamin and pyridoxine. These findings show that not only BAC and plasma folate levels, but

also plasma levels of riboflavin influence HCY plasma levels in alcohol-dependent patients.

Publications

Semmler A, Heese P, Stoffel-Wagner B, Muschler M, Heberlein A, Bigler L, Prost JC, Frieling H, Kornhuber J, Banger M, Bleich S, Hillemacher T and **Linnebank M** (2015) Alcohol abuse and cigarette smoking are associated with global DNA hypermethylation: results from the German Investigation on Neurobiology in Alcoholism (GINA). *Alcohol*, 49(2) :97-101

Haschemi Nassab M, Rhein M, Heese P, Glahn A, Frieling H, **Linnebank M**, Bleich S, Kornhuber J, Heberlein A, Grallert H, Peters A, Rawal R, Strauch K and Hillemacher T (2015) No association between the ALDH2 promoter polymorphism rs886205, alcohol dependence. *Psychiatric Genetics*, 25(1):41-2

Bleich S, Semmler A, Frieling H, Thumfart L, Muschler M, Hillemacher T, Kornhuber J, Kallweit U, Simon M and **Linnebank M** (2014) Genetic variants of methionine metabolism and DNA methylation. *Epigenomics*, 6(6): 585-91

Heese P, **Linnebank M**, Semmler A, Muschler MA, Heberlein A, Frieling H, Stoffel-Wagner B, Kornhuber J, Banger M, Bleich S and Hillemacher T (2012) Alterations of homocysteine serum levels during alcohol withdrawal are influenced by folate and riboflavin: results from the German Investigation on Neurobiology in Alcoholism (GINA). *Alcohol and Alcoholism*, 47(5): 497-500

Lenz B, Soehngen C, **Linnebank M**, Heberlein A, Frieling H, Kornhuber J, Hillemacher T and Bleich S (2009), Genetic polymorphisms relevant for one-carbon metabolism show no effect on homocysteine plasma levels and DNA methylation in alcoholism. *Psychiatric Genetics*, 19(4): 215-6

Hillemacher T, Frieling H, Moskau S, Muschler MA, Semmler A, Kornhuber J, Klockgether T, Bleich S and **Linnebank M** (2008) Global DNA methylation is influenced by smoking behaviour. *European Neuropsychopharmacology*, 18(4):295-8

Theses and Awards

Annemarie Heberlein - Thesis for associate professorship ("Habilitation" in Germany)

Is brief personalized feedback effective in reducing alcohol-related problems amongst university students in different European countries? (2007) (EA 07 08)

Moreira T, School of Health and Social Care, Oxford Brookes University, Oxford, UK

Students' drinking behaviour is influenced by youth (mis)perceptions of how their peer's drink. Young people tend to over-estimate peer group drinking levels. If misperceptions can be corrected, young people may drink less. This research investigated personalised normative feedback to correct misperception of peer drinking levels by providing information about personal drinking levels and patterns compared with norms in similar aged peer groups. Personalised normative feedback is intended to raise motivation for behaviour change. However, results of this trial show that personalised normative feedback was not effective in a UK student population. These results failed to replicate the positive findings recorded elsewhere.

This research also involved a systematic review based on 22 controlled trials involving 7,275 college or university students. The students were randomly assigned to the social norms intervention or a control group. Interventions delivered using the web or computer, or in individual face-to-face sessions, appeared to reduce alcohol misuse. The evidence was less convincing for group face-to-face sessions. Mailed and group feedback were on the whole no different than with the control intervention. Also, interventions using social norms marketing campaigns appeared not to be effective.

Publications

Moreira MT, Oskrochi R and Foxcroft DR (2012) Personalised normative feedback for preventing alcohol misuse in university students: Solomon three-group randomised controlled trial. *PLoS ONE*, 7(9):e44120

Moreira MT, Smith LA and Foxcroft DR (2009) Social norms interventions to reduce alcohol misuse in university or college students (review). *Cochrane Database of Systematic Reviews*, 8;(3):CD006748

Moreira MT and Foxcroft DR (2008) The effectiveness of brief personalized normative feedback in reducing alcohol-related problems amongst university students: protocol for a randomized controlled trial. *BMC Public Health*, 8:113

A psychosocial intervention to reduce high-risk single-session alcohol (binge) drinking among company employees in a workplace setting in four European nations (2007) (EA 07 10)

Hagger MS, School of Psychology, University Nottingham, Nottingham, UK; now with Curtin University, Australia

This research aimed at evaluating the effectiveness of theory-based interventions using motivational and implemental strategies to reduce binge drinking behaviour among students and young employees in the workplace. Two different psychological strategies were tested; a motivational strategy using mental imagery to increase the participants' intentions to reduce binge drinking behaviour, and an implemental strategy using planning to help participants carry out their intentions in situations where they are likely to binge drink. The strategies were tested in students and employees in four European countries; Estonia, Finland, Sweden and the UK. Both printed and online communication of the intervention was effective however, the strength of the effects were comparatively weak and more investigation is required to demonstrate the universality and moderating factors that lead to successful alcohol reduction.

Publications

Hagger MS, Lonsdale A, Koka A, Hein V, Pasi H, Lintunen T and Chatzisarantis NLD (2012) An intervention to reduce alcohol consumption in undergraduate students using implementation intentions and mental simulations: a cross-national study. *International Journal of Behavioral Medicine*, 19(1):82-96

Hagger MS, Lonsdale AJ and Chatzisarantis NLD (2012) A theory-based intervention to reduce alcohol drinking in excess of guideline limits among undergraduate students. *British Journal of Health Psychology*, 17(1):18-43

Hagger MS, Lonsdale A, Hein V, Koka A, Lintunen T, Pasi H, Lindwall M, Rudolfsson L and Chatzisarantis NLD (2011) Predicting alcohol consumption and binge drinking in company employees: An application of planned behaviour and self-determination theories. *British Journal of Health Psychology*, 17(2):379-407

Hagger MS, Lonsdale A and Chatzisarantis NLD (2011) Effectiveness of a brief intervention using mental simulations in reducing alcohol consumption in corporate employees. *Psychology, Health and Medicine*, 16(4):375-392

Extending growth mixture modelling for the longitudinal study of adolescent alcohol use (2007) (EA 07 12)

Percy A, Institute of Child Care Research, Queens University, Belfast, UK

In recent years there has been a growing interest among researchers in using growth mixture modelling (GMM) techniques in social and psychological sciences, in part due to advances in, and availability of, computer software designed for this purpose. The general aim of this study was to test, replicate and extend these techniques in the study of adolescent alcohol use.

Specific empirical analyses were undertaken including:

- extending GMM to include predictors of the various latent trajectory classes;
- evaluating the direct or mediating influences of various contextual factors on the development of teenage alcohol use;
- examining the association of putative risk factors, time independent covariates from multiple domain and trajectory group membership in zero-inflated mixture modelling, and;
- using a genetic relationship matrix generated from a multigenerational pattern of substance use to obtain more robust parameter estimates and to examine the proportionate contributions of genes and environment to substance use development and subsequent abuse.

The results showed that the shared environmental influences of family non-shared environmental effects accounted about 0.97 percent of total variance of alcohol use. Growth curve modelling explicitly considers both intra-individual change and inter-individual differences in alcohol use and delinquency disorder. The assumption of homogeneity in the growth parameters for alcohol use and delinquency disorder is unrealistic. It is emphasised that statistical analyses and their effects can be seriously biased if heterogeneity is ignored.

Publications

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The bidirectional relationship between the biological clock and alcohol addiction (2007) (EA 07 14)

Jacobs EH, Department of Cell Biology and Genetics, Erasmus University Medical Center, Rotterdam, The Netherlands

The biological clock regulates diverse processes such as behaviour, physiology and metabolism. The clockwork consists of genes that switch each other on and off with a periodicity of about 24 hours and is hence called a circadian oscillator. Organisms keep up with the daily light-dark rhythm of 24 hours by light-mediated adjustment of their internal clock to this rhythm. The biological clock is an important factor in proper mammalian functioning. There are many examples of disturbances of the clock, such as shift work, trans- meridian flights resulting in jet lag, ageing and genetic disturbances of the clockwork. Malfunctioning of this system may well play a role in a wide array of diseases, such as cancer, psychiatric and neurological disorders. This project investigated, in mouse models with a circadian defect, how a disturbed biological clock may affect alcohol consumption. It seems that for alcohol consumption and preference an intact circadian oscillator is not required, but it may be important for the *motivation* to receive alcohol. How alcohol consumption might change the performance of the biological clock was also investigated. It appeared that alcohol consumption does not change the clock itself, but it diminishes the clock resetting effect of light.

Publications

Papachristos EB, **Jacobs EH** and Elgersma Y (2011) Interval timing is intact in arrhythmic Cry1/Cry2-deficient mice. *Journal of Biological Rhythms*, *26*(4):305-313

'Blind Drunk?' Differentiating the Psychopharmacological and Expectancy Effects of Alcohol Consumption on Attentional Bias (2007) (EA 07 15)

Albery I, Department of Psychology, London South Bank University, London, UK

Attentional biases, the phenomenon whereby individuals find they are distracted by objects or information that is relevant to them, have been consistently demonstrated in alcohol consumption and drug use in laboratory studies. This research investigated attentional bias among social drinkers in an alcohol-related environment (i.e. a pub).

Results showed that both actual and expected alcohol consumption did not affect attentional biases for alcohol-related stimuli. The extent to which individuals demonstrate these biases may vary depending on whether they are drinking, and whether they are in a drinking-related setting or not.

Findings suggest that attentional bias is a more complex phenomenon than earlier suggested by laboratory research. Interventions for dependent users that are aimed at manipulating these biases should proceed cautiously until the mechanisms are more clearly elucidated.

Publications

Albery IP, Sharma D, Noyce S, Frings D and Moss AC (2015) Testing a frequency of exposure hypothesis in attentional bias for alcohol-related stimuli amongst social drinkers. *Addictive Behaviors Reports*, 68-72 (ERAB funding not acknowledged)

Molecular and cellular damage induced by "Binge drinking" in adolescents. Can this be diminished by targeted protaurine drugs? (2007) (EA 07 23)

Della Corte L, Department of Preclinical and Clinical Pharmacology, University Firenze, Firenze, Italy

Binge drinking can induce adverse effects in specific brain regions, especially in female susceptible individuals. This research investigated these effects of binge

drinking by using an adolescent female rat model. The results show that binge drinking induces inflammation leading to changes in specific cells to release damaging compounds. This causes brain damage in a specific brain region, the hippocampus. This may be responsible for the memory deficits, which occur in susceptible individuals after taking alcohol in such a fashion. The use of specific compounds which prevent inflammation may stop such damaging changes in the brain in an animal model but binge drinking in humans should be discouraged.

Publications

Stefanini C, Colivicchi MA, **Della Corte L**, Ward RJ, De Witte P, Lallemand F, Hemmings K, Pitard A, Page MI, Nayak K and Dexter DT (2014) Ethane-b-sultam modifies the activation of the innate immune system induced by intermittent ethanol administration in female adolescent rats. Journal of *Alcoholism & Drug Dependence*, 2(2)

Ward RJ, Lallemand F, De Witte P, Crichton RR, Piette J, Tipton K, Hemmings K, Pitard A, Page M, **Della Corte L**, Taylor D and Dexter D (2011) Anti-inflammatory actions of a taurine analogue, ethane b-sultam, in phagocytic cells, *in vivo* and *in vitro*. *Biochemical Pharmacology*, 81(6):743-751

Lallemand F, Ward RJ and De Witte P (2009) The influence of chronic nicotine administration on behavioural and Neurochemical parameters in male and female rats after repeated binge drinking exposure. *Alcohol and Alcoholism*, 44(6):535-546

Ward RJ, Lallemand F and De Witte P (2009) Biochemical and neurotransmitter changes implicated in alcohol induced brain damage in chronic or 'binge drinking' alcohol abuse. *Alcohol and Alcoholism*, 44(2):128-135

Ward RJ, Colivicchi MA, Allen R, Schol F, Lallemand F, De Witte P, Ballini C, **Della Corte L** and Dexter D (2009) Neuro-inflammation induced in the hippocampus of "binge drinking" rats may be mediated by elevated extracellular glutamate content. *Journal of Neurochemistry*, 111(5):1119-1128

Freinbichler W, Tipton KF, **Della Corte L** and Linert W (2009) Mechanistic aspects of the Fenton reaction under conditions approximated to the extracellular fluid. *Journal of Inorganic Biochemistry,* 103(1), 28-34

Petkova-Kirova P, Rakovska A, Zaekova G, Ballini C, **Della Corte L**, Radomirov R and Vágvölgyi A (2008) Stimulation by neurotensin of dopamine and 5-hydroxytryptamine (5-HT) release from rat prefrontal cortex: possible role of NTR1 receptors in neuropsychiatric disorders. *Neurochemistry International*, 53(6-8), 355-361

Theses and Awards

Dr. Chiara Stefanini - PhD

Characterization of the role of immune mechanisms in the progression of alcoholic liver disease (2008) (EA 08 05)

Albano, E. University "A. Avogadro" of East Piedmont, Novara, Italy

It is increasingly recognized that inflammation has an important role in the pathogenesis of alcoholic liver disease (ALD). Nonetheless, the mechanisms by which alcohol maintains hepatic inflammatory processes are still incompletely characterized. In this context, the possible role of adaptive immunity has emerged from evidence of lymphocytes recruitment and activation in the inflammatory infiltrates of ALD. This project aimed at evaluating the actual contribution of oxidative stress-mediated immunity in the development of alcohol liver injury. Animal studies were performed where alcohol-fed mice were pre-immunized with protein-adducts with different lipid peroxidation products. Among the different immunization protocols the use of MDA-adducts was the most effective. As compared to non-immunized mice, upon alcohol exposure, MDA-sensitized animals developed more severe liver injury characterized by diffuse lymphocyte infiltration. The hepatic production of pro-inflammatory cytokines/chemokines TNF-α, IL-12, CCL2 was also significantly increased in immunized alcohol-fed animals. Altogether these results indicated that the stimulation of humoral immunity by antigens that are generated by oxidative stress, can contribute to promoting inflammatory reactions during the development of alcoholic liver injury. However, they did not rule out the possibility that cellular immunity might also contribute to chronic inflammation in ALD.

Publications

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Risk factors for alcohol binge drinking in native adolescents and immigrants in Germany (2008) (EA 08 06)

Hillemacher T, Klinik fûr Psychiatrie, Sozialpsychiatrie und Psychotherapie, Hannover, Germany

This research was aimed at determining the prevalence of risky alcohol consumption patterns (binge drinking) in German adolescents. Differences in drinking behaviour between adolescents from different backgrounds were also investigated. Additionally, protective and risk factors for binge drinking among German adolescents were explored. The results indicated that binge drinking is a common problem behaviour in German adolescents. Binge drinking is more common among adolescents in rural areas. Adolescents with Turkish roots showed less binge drinking than adolescents of German or Russian descent. Next to that, the two most influential factors found to protect against binge drinking were low economic status and importance of religion. The four most relevant risk factors for binge drinking were life-time prevalence of school absenteeism/truancy, academic failure, suicidal thoughts, and violence at school.

Publications

Donath C, Graessel E, Baier D, Bleich S and **Hillemacher T** (2014) Is parenting style a predictor of suicide attempts in a representative sample of adolescents? *BMC Pediatrics*, 14:113

Donath C, Grässel E, Baier D, Pfeiffer C, Bleich S and **Hillemacher T** (2012) Predictors of binge drinking in adolescents: ultimate and distal factors – a representative study. *BMC Public Health*, 12:263

Donath C, Grässe E, Baier D, Pfeiffer C, Karagülle D, Bleich S and **Hillemacher T** (2011) Alcohol consumption and binge drinking in adolescents: comparison of different migration backgrounds and rural vs. urban residence – a representative study. *BMC Public Health*, 11:84

Karagülle D, Donath C, Bleich S and **Hillemacher T** (2010) Rauschtrinken bei Jugendlichen und jungen Erwachsenen. *Fortschritte der Neurologie - Psychiatrie,* 78(4):196-202

Theses and Awards

Dr. Carolin Donath - PhD

Dr. Hillemacher - ERAB Travel Award 2007

Alcohol-induced changes in learning bias: a possible 'gateway' to drug addiction (2008) (EA 08 12)

Ripley TL, University of Sussex, Falmer, Brighton, UK

This series of experiments used a mouse model to look at the long-term effect of binge intoxication on attentional processes, which may impact upon future behaviours including drug taking. Three important findings were made. Firstly, binge intoxication leads to a shift in attentional processes, such that animals now favour local cues over global cues in a spatial learning task. If this shift or narrowing of focus is also true in other tasks, it may mean that animals are more prone to conditioning processes where local cues indicate the availability of a natural or drug reward. Indeed, the second finding suggested that this is true. Animals that had been exposed to binge intoxication were more likely to approach a discrete cue that had been associated with ethanol when compared with a control group. Finally, a more sophisticated task was used to look at this type of behaviour. Animals naturally have a greater or lesser tendency to approach environmental stimuli associated with rewards. Those animals that had a natural tendency to approach discrete cues associated with a reward (Pavlovian approach – sign trackers) did so to a far greater extent if they had previously been exposed to ethanol in a binge pattern.

Together these results suggest that binge ethanol exposure leads to long-term changes in attentional focus, with some cues taking on greater salience than normal. As it is known that these types of cues are particularly important in drug addiction, both during consumption and relapse phases, it is possible that a pattern of binge intoxication may increase vulnerability to future drug taking behaviour.

Publications

Ripley TL and Stephens DN (2011) Critical thoughts on current rodent models for evaluation potential treatments of alcohol addiction and withdrawal. *British Journal of Pharmacology*, 164:1335-1356

Effects of Alcohol on Rating of Attractiveness: Examining the role of alcohol in social interaction (2008) (EA 08 20)

Munafò MR, School of Psychological Science, University of Bristol, Bristol, UK

This research conducted a series of human laboratory experiments to explore the effect of alcohol on emotion processing. The research also investigated the effect of alcohol on ratings of attractiveness, both by the consumer of other individuals, (i.e., intoxicated people viewing sober people), and by other individuals of the consumer (i.e., sober people viewing intoxicated people). Additionally, the possible moderating influence of social and contextual cues to sexual behaviour on the effects of alcohol was investigated. The results indicated that the effects of alcohol on ratings of attractiveness may not be isolated to the consumer. It is possible that low levels of alcohol consumption may influence attractiveness of the consumer, either through changes in face shape (e.g., resulting from muscle relaxation) or facial colouration (consistent with evidence that faces with a modest degree of red colouration are rated as more attractive than more pallid faces).

Publications

Van Den Abbeele J, Penton-Voak IS, Attwood AS, Stephen ID and **Munafò MR** (2015) Increased facial attractiveness following moderate, but not high, alcohol consumption. *Alcohol and Alcoholism*, 50(3):296-301

Penton-Voak IS, Cooper RM, Roberts RE, Attwood AS and **Munafò MR** (2012) Effects of acute alcohol consumption on the perception of eye gaze direction. *Journal of Psychopharmacology*, 26(2):254-261

Theses and Awards

Dr. Munafò - ERAB Travel Award 2005

Effects of moderate alcohol consumption on gene expression in subcutaneous adipose tissue in lean and overweight postmenopausal women (2008) (EA 08 21)

Hendriks H, Business Unit Biosciences, TNO Quality of Life, AJ Zeist, The Netherlands

Moderate alcohol consumption has various acute and longer-term effects on low-grade inflammation which may accumulatively affect chronic disease risk. This research provided insights of how moderate alcohol consumption might exert its effect to reduce inflammatory processes in the body by combining and integrating several sophisticated techniques. An integrated approach of large-scale profiling of proteins and genes in blood showed that longer-term moderate alcohol consumption altered several important processes related to signalling, immune response and lipid metabolism. Additionally, results showed that both total and high-molecular weight adiponectin concentrations are higher after moderate alcohol consumption compared with abstention in premenopausal women. These effects were evident after at least three weeks of consumption and occurred concomitantly. Adiponectin is a hormone solely secreted by adipose tissue. It predicts insulin sensitivity. Low levels of this hormone are also predictive for type 2 diabetes. This study showed that moderate alcohol consumption can increase both the total and the high-molecular form adiponectin in younger, normal-weight women. At least three weeks of moderate drinking were necessary to have these effects.

Publications

Joosten MM, van Erk MJ, Pellis L, Witkamp RF and **Hendriks HFJ** (2011) Moderate alcohol consumption alter both leucocyte gene expression profiles and circulating proteins related to immune response and lipid metabolism in men. *British Journal of Nutrition*, 108(4):620-627

Joosten MM, Witkamp RF and **Hendriks HFJ** (2011) Alterations in total and high-molecular-weight adinopectin after 3 weeks of moderate alcohol consumption in premenopausal women. *Metabolism: Clinical and Experimental*, 60(8):1058-1063

Theses and Awards

Dr. Michel Joosten – PhD (2010) Moderate alcohol consumption, adiponectin, inflammation and type 2 diabetes risk - Prospective cohort studies and randomized crossover trials. Thesis number: ISBN 978-90-8585-825-6

The reduction of adolescent alcohol misuse: examining the potential universal effects of a targeted prevention programme (2008) (EA 08 22)

Mackie C, King's College London, UK

Alcohol misuse by young people is a significant and escalating problem in Europe. Delaying the onset of adolescent drinking would have a major impact on reducing both the social and health costs associated with adolescent alcohol misuse. Universal prevention programmes that target the general adolescent population have been met with limited success.

Findings of this study suggested that focused interventions that target individuals who show a heightened risk for alcohol misuse also result in reduced alcohol use among low-risk students attending the same schools. This is due to fewer drinking opportunities and a reduction in alcohol use by their high-risk friends. Further analysis planned to examine whether peer influence can explain the reduction in low-risk students alcohol use.

The implication of this study is that by reducing opportunities for alcohol use and attitudes surrounding drinking behaviours, the targeted intervention might transfer its effects to the general adolescent population.

Publications

Conrod PJ, O'Leary-Barrett M, Newton N, Topper L, Castellanos-Ryan N, **Mackie CJ** and Girard A (2013) Effectiveness of a Selective, Personality-Targeted Prevention Program for Adolescent Alcohol Use and Misuse A Cluster Randomized Controlled Trial. *JAMA Psychiatry,* 70(3):334-342

Mackie CJ, O'Leary-Barrett M, Al-Khudhairy N, Castellanos Ryan N, StruveM, Topper L and Conrod P (2012) Adolescent bullying, cannabis use and emerging psychotic experiences: A longitudinal general population study. Psychological Medicine, 43(5):1033 – 1044. DOI: https://doi.org/10.1017/S003329171200205X

Alcohol Consumption and Mortality Risk among Patients with Cardiovascular Disease: a Meta-Analysis and a Longitudinal Study on Patients with Coronary Artery Disease Undergoing Surgical Revascularization (2008) (EA 08 27)

de Gaetano G, Università Cattolica del Sacro Cuore, Centro di Ricerche e Formazione ad Alta Tecnologia nelle Scienze Biomediche, Campobasso, Italy.
Present address: Department of Epidemiology and Prevention, IRCCS Neuromed, Pozzilli, Italy

This research project aimed at investigating the association between alcohol consumption and mortality risk in subjects with previous cardiovascular disease (CVD). Results of a large meta-analysis and a review show that light to moderate alcohol consumption is significantly associated with a lower incidence of cardiovascular and all-cause mortality in patients with CVD. Additionally, the project investigated, in a pilot study, the association between alcohol consumption and short and long-term prognosis after surgical revascularization (CABG). Results showed no significant differences in the major outcomes in relation to alcohol intake, possibly due to the small patient sample examined. The feasibility of a larger study was checked, to improve the power of the study and to investigate the relationship between alcohol consumption and short-term outcomes (especially atrial fibrillation) among coronary artery disease patients undergoing coronary artery bypass graft. This research showed that the beneficial effect of moderate alcohol consumption on cardiovascular risk does apply not only to healthy people but also to patients with a history of ischaemic heart disease. Thus, alcohol in moderation may contribute to both primary and secondary prevention of cardiovascular disease.

Publications

Costanzo S, De Curtis A, di Niro V, Olivieri M, Morena M, De Filippo CM, Caradonna E, Krogh V, Serafini M, Pellegrini N, Donati MB, **de Gaetano G** and Iacoviello L; Polyphemus Observational Study Investigators (2015) Postoperative atrial fibrillation and total dietary antioxidant capacity in patients undergoing cardiac surgery: The Polyphemus Observational Study. *Journal of Thoracic and Cardiovascular Surgery,* 149(4):1175-82.e1

Costanzo S, Di Castelnuovo A, Benedetta Donati M, Iacoviello L and **de Gaetano G** (2011) Alcohol consumption in relation to vascular and total mortality in patients with diabetes, hypertension or history of cardiovascular disease: a meta-analysis. *Journal of Wine Research*, 22(2):119-122

Costanzo S, Di Castelnuovo A, Benedetta Donati M, Iacoviello L and **de Gaetano G** (2010) Alcohol consumption and mortality in patients with cardiovascular disease: a meta-analysis. *Journal of American College of Cardiology*, 55(13):1339-1347

Costanzo S, Di Castelnuovo A, Benedetta Donati M, Iacoviello L and **de Gaetano G** (2010) Cardiovascular and overall mortality risk in relation to alcohol consumption in patients with cardiovascular disease. *Circulation*, 121(17):1951-1959

Theses and Awards

Dr. Augusto Di Castelnuovo - PhD 2010

Dr. Simona Costanzo - PhD 2012 Alcohol consumption in relation to cardiovascular risk and mortality.

Longitudinal study of social and cognitive risks for alcohol misuse in first year university students (2009) (EA 09 04)

Moore S, Violence and Society Research Group, Cardiff University, Cardiff, UK

This research assessed the barriers, acceptability and validity of text messaging to collect daily alcohol consumption data among young people transitioning from school to university. University life is perceived as strongly associated with alcohol use. However, alcohol perceptions are far from stable. As drinkers move across contexts, the perceived acceptability of alcohol can change. The research also explored the feasibility of a text-delivered intervention. Results showed that greater alcohol use was observed on Fridays, Saturdays and Wednesdays as well as notable celebratory events. Interview data indicated that text messaging was acceptable to participants and preferred over email and web-based methods. Additionally results suggested that this approach can be developed as a surveillance tool to collect high frequency consumption data to identify periods of vulnerability and that it can offer a platform through which targeted interventions can be delivered.

Publications

Moore SC, Crompton K, van Goozen S, van den Bree MBM, Bunney J and Lydall E (2013) A feasibility study of short message service text messaging as a surveillance tool for alcohol consumption and vehicle for interventions in university students. *BMC Public Health*, 13:1011

Moore SC (2010) Substitution and complementary in the face of alcohol-specific policy interventions. *Alcohol and Alcoholism*, 45(5):403-408

The role of alcohol consumption in the aetiology of lymphatic malignancies (2009) (EA 09 10)

Verhage BAJ, Department of Epidemiology, University of Maastricht, Maastricht, The Netherlands

Results from epidemiological studies suggest that alcohol drinkers may have a decreased risk of lymphoid neoplasms whereas results for myaloidal neoplasms are inconsistent. This research examined the association between alcohol consumption and hematologic malignancies; a group of neoplasms arising in lymphoid and myeloid cells throughout the body. Data from a large prospective cohort on diet and cancer in men and women in the Netherlands was used. The results did not show a clear association between alcohol consumption and lymphoid and myeloid neoplasms. No associations were found for specific alcohol beverages either. The study did not find an association between other dietary factors and the risk of lymphoid and myeloid neoplasms. Additionally, alcohol did not seem to modify the association between folate and these neoplasms.

Publications

Heinen MM, van den Brandt PA, Schouten LJ, Goldbohm RA, Schouten HC and **Verhage BAJ** (2014) Dietary one-carbon nutrient intake and risk of lymphoid and myeloid neoplasms: results of the Netherlands cohort study. *Cancer Epidemiology, Biomarkers and Prevention*, 23(10):2153-2164

Heinen MM, **Verhage BAJ**, Schouten LJ, Goldbohm RA, Schouten HC and van den Brandt PA (2013) Alcohol consumption and risk of lymphoid and myeloid neoplasms: results of the Netherlands cohort study. *International Journal of Cancer*, 133(7):1701-1713

Training executive functions to reduce alcohol abuse: restoring control over automatic impulses to drink alcohol (2009) (EA 09 13)

Houben K, Faculty of Psychology and Neuroscience, University of Maastricht, Maastricht, The Netherlands

The hypothesis of this research project was that training working memory and response inhibition increases executive control over automatic impulses to drink alcohol and that training these executive functions may decrease alcohol use. The results from different studies showed that training working memory (the ability to maintain goal-relevant information) and response inhibition may be effective strategies to reduce alcohol use by increasing control over automatic impulses to drink alcohol. Integrating such training programs with online cognitive and motivational interventions could improve helping self-selected problem drinkers to reduce their drinking.

Publications

Wiers RW, **Houben K**, Fadardi JS, van Beek P, Rhemtulla M and Cox WM (2015) Alcohol cognitive bias modification training for problem drinkers over the web. *Addictive Behaviors*, 40:21-26

Houben K, Havermand RC, Nederkoorn C and Jansen A (2012) Beer à no-go: learning to stop responding to alcohol cues reduces alcohol intake via reduced affective associations rather than increase response inhibition. *Addiction*, 107(7):1280-1287

Houben K, Wiers RW and Jansen A (2011) Getting a grip on drinking behavior: training working memory to reduce alcohol abuse. *Psychological Science*, 22(7):968-975.

Houben K, Nederkoorn C, Wiers RW and Jansen A (2011) Resisting temptation: decreasing alcohol-related affect and drinking behavior by training response inhibition. *Drug and Alcohol Dependence*, 116(1-3):132-136

Houben K (2010) Stoppen met drinken kan je leren: 'Een impulsieve en een reflectieve route naar gedragsverandering'. *Psychologie en Gezondheid*, 38(4):153-162

Theses and Awards

Dr. Katrin Houben - Associate Professorship and ERAB Publications Award 2015

Analysis of the molecular mechanisms of the synergistic effect of chronic alcohol consumption and obesity on the development and progression of hepatic steatosis, steatohepatitis and fibrosis (2009) (EA 09 20)

Stickel F, Institute if Clinical Pharmacology and Visceral Research, University of Bern, Bern, Switzerland

The aim of this research was to establish and analyse an experimental animal model to investigate the combined effect of chronic alcohol administration and a high-fat diet on liver injury. The first series of animal experiments established a novel animal model of chronic alcohol administration and diet-induced fatty liver, and found an additive effect of either condition on liver fat content, hepatitis activity and liver tissue scarring in mice. This new model will allow the investigation of isolated or joint effects of alcohol and HF diet on hepatic injury, where alcohol and HF diet appear to act synergistically on the development of hepatic fibrosis. The next steps of this research are to focus on therapeutic inventions with the potential to offset these effects.

Publications

Mahli A, Thasler WE, Patsenker E, Müller S, **Stickel F**, Müller M, Seitz HK, Cederbaum AI and Hellerbrand C (2015) Identification of cytochrome CYP2E1 as critical mediator of synergistic effects of alcohol and cellular lipid accumulation in hepatocytes *in vitro*. *Oncotarget*, 6:41464-78

Patsenker E, Stoll M, Millonig G, Agaimy A, Wissniowski T, Schneider V, Mueller S, Brenneisen R, Seitz HK, Ocker M and **Stickel F** (2011) Cannabinoid receptor type I modulates alcohol-induced liver fibrosis. *Molecular Medicine*, 17(11-12):1285-1294

Gäbele E, Dostert K, Dorn C, Patsenker E, **Stickel F** and Hellerbrand C (2011) A new model of interactive effects of alcohol and high-fat diet on hepatic fibrosis. *Alcohol: Clinical and Experimental Research*, 35(7):1361-1367

Stickel F and Seitz HK (2010) Alcoholic steatohepatitis. *Best Practice and Research in Clinical Gastroenterology*, 24(5):683-693

Peer group influences on the relationship between depressive symptoms and substance misuse in adolescence (2010) (EA 10 08)

van den Bree MBM, Department of Psychological Medicine, University of Wales, Cardiff, Wales, UK

The study found that adolescents who suffered from depressed mood in mid adolescence were at higher risk of having alcohol problems in late adolescence as well as in early adulthood. This link was indirect as adolescents who experienced depressed mood in mid-adolescence were more likely to become friends with peers who engaged in substance use and delinquent activities (i.e., shoplifting, setting things on fire). Engaging with this peer group, subsequently, increased the risk of problem alcohol use in late adolescence and early adulthood. Adolescents with low mood who do not form such relationships may not develop alcohol problems. Similarly, the study found that adolescents who engage in problem alcohol use in mid adolescence were more likely to experience depressed mood in late adolescence if they affiliated with deviant friends who engaged in delinquent activities or substance use. The study found that high levels of parental monitoring (e.g., having to ask for permission before going out) could reduce the impact of a deviant peer group on the development of problem alcohol use in adolescents suffering from depressed mood. The results also showed that sexual minority adolescents were more likely to drink heavily in early adulthood (at age 18) than adolescents who identified as heterosexuals. The risk of alcohol problem use in this group was partly due to high levels of depressed mood experienced by these youths in late adolescence.

Publications

Pesola F, Shelton KH, Heron J, Munafo M, Hickman M and **van den Bree MBM** (2015) The developmental relationship between depressive symptoms in adolescence and harmful drinking in emerging adulthood: the role of peers and parents. *Journal of Youth and Adolescence*, 44(9):1752-66

Pesola F, Shelton KH, Heron J, Munafo M, Maughan B, Hickman M and **van den Bree MBM** (2015) The mediating role of deviant peers on the link between depressed mood and harmful drinking. *Journal of Adolescent Health*, 56(2):153-159

Pesola F, Shelton KH and **van den Bree MBM** (2014) Sexual orientation and alcohol problem use among UK adolescents: an indirect link through depressed mood. *Addiction*, 109(7):1072-1080

Theses and Awards
Dr. Luca Saraceno - PhD 2010
Dr. Roland Jones - PhD 2015
Dr. Jennifer Ware - PhD 2012
Dr. Alegra Hummel - PhD 2013

Changing the vulnerable brain: a neuromodulation study in alcohol dependence (2010) (EA 10 27)

Goudriaan A E, University of Amsterdam, Amsterdam UMC, Department of Psychiatry, location Meibergdreef, and Arkin Amsterdam, The Netherlands

Abstinence is one of the main goals of addiction treatment, but over 50% of alcohol dependent patients relapse within the first year. Relapse has been related to craving and impaired processing of emotional information. The results of this project indicated that alcohol dependent patients have reduced activation in the brain during an emotion regulation task, and that the higher craving can be reduced by applying Repetitive Transcranial Magnetic Stimulation (rTMS). Non-invasive brain stimulation techniques like rTMS can reduce craving levels as reported in this meta-analysis. In addition, rTMS can increase the ability to regulate negative emotions. This indicates that rTMS may be clinically relevant and that the study of rTMS as an intervention for alcohol dependence should be focused on in future intervention studies.

Publications

Schluter RS, Jansen JM, van Holst RJ, van den Brink W and **Goudriaan AE** (2018) Differential effects of left and right prefrontal high-frequency repetitive transcranial magnetic stimulation on resting-state functional magnetic resonance imaging in healthy individuals. *Brain Connectivity,* 8(2): 60-67

van Timmeren T, Jansen JM, Caan MW, **Goudriaan AE** and van Holst RJ (2016) White matter integrity between left basal ganglia and left prefrontal cortex is compromised in gambling disorder. *Addiction Biology,* 22(6):1590-1600

Jansen JM, van Wingen G, van den Brink W and **Goudriaan AE** (2015) Resting state connectivity in alcohol dependent patients and the effect of repetitive transcranial magnetic stimulation. *European Neuropsychopharmacology*, 25(12):2230-2239

Jansen JM, van Holst RJ, van den Brink W, Veltman DJ, Caan MWA and **Goudriaan AE** (2015) Brain function during cognitive flexibility and white matter integrity in

alcohol-dependent patients, problematic drinkers and healthy controls. *Addiction Biology*, 20(5):979-989

Goudriaan AE (2014) Stepping up the game. *Addiction*, 109(9):1409-1413

Jansen JM, Daams JG, Koeter MWJ, Veltman DJ, van den Brink W and **Goudriaan AE** (2013) Effects of non-invasive neurostimulation on craving: a meta-analysis. *Neuroscience and Biobehavioral Reviews*, 37(10):2472-2480

Theses and Awards

Proffessor Dr. Goudriaan – ERAB Publications Award 2018

Dr. Jochem M. Jansen - PhD 2016

Binge drinking: Cognitive and brain impairment and their association with immune response (2010) (EA 10 30)

Campanella S, Medical Psychology Laboratory, Brugmann Hospital ULB, Brussels, Belgium

This study investigated the effect of binge drinking on the brain in university students in relation to the immune response. It identified subtle differences in various cognitive tests, which relate primarily to possible alcohol-induced changes in the frontal brain regions.

Binge drinking, especially in adolescents, can induce progressive activation of the immune system. Related to that, an increase in pro-inflammatory mediators may lead to modifications of specific brain functions. Binge drinking also alters cognitive performance, because of changes in the brain that facilitate normal behavioural performance. More insight into the association between neuro-cognitive impairments and neuro-inflammation would help to identify adolescents at risk from cognitive impairment and educate and advise such individuals as there is substantial evidence that long term chronic alcoholism may ensue. Binge alcohol consumption leads to changes in cerebral responses that may be considered as vulnerability factors for developing adult substance use disorders.

Publications

Stefanini C, Colivicchi M A, Della Corte L, Ward RJ and De Witte P (2014) Ethane-β-Sultam Modifies the Activation of the Innate Immune System Induced by Intermittent Ethanol Administration in Female Adolescent Rats. *Journal of Alcoholism and Drug Dependence*, 2(2):150

Ward RJ, Lallemand F and De Witte P (2014) Influence of adolescent heavy session drinking on the systemic and brain innate immune system. *Alcohol and Alcoholism*, 49(2):193-197

Lallemand F, Ward RJ, De Witte P, Petit G, Saeremans M, Verbanck P, Noël X and **Campanella S** (2013) Changes in the Innate Immune Responses by Intermittent Ethanol Consumption May Influence Cognition in Susceptible Adolescent Binge Drinkers. *Journal of Alcoholism and Drug Dependence*, 1:114-119

Campanella S, Peigneux P, Petit G, Lallemand F, Saeremans P, Noël X, Metens T, Nouali M, De Tiège X, De Witte P, Ward RJ and Verbanck P (2013) Increased cortical activity in binge drinkers during working memory task: a preliminary assessment through a functional magnetic resonance imaging study. *PLoS ONE*, 8(4), e6220

Ward R, De Witte P, Lallemand F, Noël X, **Campanella S** and Verbank P (2011) S14. 3 Can Peripheral Markers Indicate Neuroinflammation? *Alcohol and Alcoholism*, 46(suppl_1), i13-i14

Role of BDNF signalling in alcohol abuse: new insights from a yoked paradigm (2010) (EA 10 34)

Orrù A, Laboratory of Experimental Psychopharmacology, Institute for Pharmacological Research Mario Negri, Milan, Italy

Pre-clinical data suggest that prolonged alcohol use may induce long-lasting structural and physiological changes in the brain. These changes may regulate the transition from social drug use to abuse and addiction. This project investigated these changes in rats in specific situations, acute and chronic alcohol exposure, abstinence and relapse. The researchers evaluated the ability of ethanol to modify gene and protein expression of specific effectors, such as brain-derived neurotrophic factor (BDNF), known to be involved in the development and manifestations of alcohol abuse. Results showed that ethanol can impact the expression of specific effectors, but it depends on certain aspects such as the brain region, the dose of ethanol, and method of drug exposure.

Publications

Orrù A, Caffino L, Moro F, Cassina C, Giannotti G, Di Clemente A, Fumagalli F and Cervo L (2016) Contingent and non-contingent recreational-like exposure to ethanol alters BDNF expression and signaling in the cortico-accumbal network differently. *Psychopharmacology*, 233(17):3149-60

Theses and Awards
Dr. Orrù - ERAB Travel Award 2009

Young people's beliefs about the benefits and risks associated with different alcoholic beverages: A comparison of the UK and France (2011) (EA 11 10)

Terry P, Department of Psychology, Kingston University, London, UK

Young adults in the UK and France have quite a limited understanding of the health consequences associated with drinking different kinds of alcoholic drink. They confuse "healthiness" (and its opposite) with issues of drink production and "naturalness"; artificial additives are widely considered to be at least as important as alcohol content when making judgments about potential adverse health effects. Next to that, the chronic effects of alcohol on health are not a serious consideration for young people in France or the UK. Alcohol's acute effects on health and well-being are recognised, but the possible long-term effects are largely overlooked because – in both countries – young people do not expect to become long-term consumers of alcohol in excess. The research demonstrated a need to make young people aware that binge-drinking, which is increasingly common in France as well as the UK, is not without long-term health risks (such as liver damage) and that these risks are not reduced by drinking beverages perceived to be healthier, e.g. wine rather than spirits.

Publications

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Theses and Awards
Dr. Victoria Barber - PhD 2016 Young people's beliefs about the health effects of different alcoholic beverages: an exploratory comparison of the UK and France

Understanding and promoting young people's strategies for moderate alcohol consumption (2011) (EA 11 11)

de Visser R, University of Sussex, Falmer, UK

In this study skills and strategies were identified that could be taught to young people to enhance their capacity to drink in moderation.
Questionnaire data suggested that there is support among young people for teaching alcohol refusal skills and strategies. Based on interviews a range of effective strategies and techniques used by young people to resist expectations to drink and direct pressure to drink were identified. These strategies and tactics were used to develop video resources. Finally, how these videos were received by young people and professionals working with young people was evaluated. This study showed that there is value in using video materials to teach young people skills and strategies to better respond to expectations to drink and direct pressure to drink. The results so far indicate support for the general approach of teaching alcohol refusal skills.

Publications

Graber R, **de Visser RO**, Abraham C, Memon A, Hart A and Hunt K (2016) Staying in the 'sweet spot': A resilience-based analysis of the lived experience of low-risk drinking and abstention among British youth. *Psychology and Health*, 31(1):79-99

de Visser RO, Hart A, Abraham C, Graber R, Scanlon T and Memon A (2014) How alike are young non-drinkers, former-drinkers, low-risk drinkers, and hazardous drinkers? *Addictive Behaviors*, 39(8):1258-1264

de Visser RO, Hart A, Abraham C, Memon A, Graber R and Scanlon T (2014) Which alcohol control strategies do young people think are effective? *Drug and Alcohol Review*, 33(2):144-151

Evaluation of a new beer biomarker to study the effects of moderate beer consumption on cardiovascular risk (2011) (EA 11 17)

Lamuela-Raventós RM, Department of Nutrition and Food Science, School of Pharmacy, University of Barcelona, Barcelona, Spain

This project first developed and validated a method for the determination of beer prenylflanavoids in human urine. Beer prenylflavanoids constitute a potential new potent biomarker of beer consumption. This method was then applied to analyse human urine from two different clinical trials to evaluate the usefulness, specificity and selectivity of the proposed new biomarker. The results show that isoxanthohumol is an effective new biomarker of beer consumption, with great sensitivity and specificity. Urinary excretion of isoxanthohumol showed dose-response behaviour.

In nutrition and food studies, nutritional biomarkers have several advantages over self-reported data, since they are more precise and provide more objective assessments than data obtained from food questionnaires. Using this new biomarker of beer intake, the possible risks and benefits of moderate beer consumption can be evaluated in human health more objectively, avoiding the bias from Food Frequency Questionnaires.

Publications

Quifer-Rada P, Vallverdu-Queralt A, Martinez-Huélamo M, Chiva-Blanch G, Jauregui O, Estruch R and **Lamuela-Raventós RM** (2015) A comprehensive characterisation of beer polyphenols by high resolution mass spectrometry (LC-ESI-LTQ-Orbitrap-MS). *Food Chemistry*, 169:336-343

Chiva-Blanch G, Magraner E, Condines X, Valderas-Martinez P, Roth I, Arranz S, Casas R, Navarro M, Hervas A, Siso A, Martinez-Huélamo M, Vallverdu-Queralt A, Quifer-Rada P, **Lamuela-Raventós RM** and Estruch R (2015) Effects of alcohol and polyphenols from beer on atherosclerotic biomarkers in high cardiovascular risk men: a randomized feeding trial. *Nutrition, Metabolism and Cardiovascular Diseases*, 25(1):36-45

Quifer-Rada P, Martinez-Huelamo M, Chiva-Blanch G, Jauregui O, Estruch R and **Lamuela-Raventós RM** (2014) Urinary isoxanthohumol is a specific and accurate biomarker of beer consumption. *The Journal of Nutrition (ASN)*, 144(4):484-488

Quifer-Rada P, Martinez-Huelamo M, Jauregui O, Chiva-Blanch G, Estruch R and **Lamuela-Raventós RM** (2013) Analytical condition setting is a crucial step in the

quantification of unstable polyphenols in acidic conditions: analysing prenylflavanoids in biological samples by LC-ESI-MS/MS. *Analytical* Chemistry, 85(11):5547-5554

Theses and Awards

Dr. Lamuela-Raventós - ERAB Publications Award 2014

Psycho-physiological paradigms as predictors of relapse in the treatment of alcohol dependent subjects (2011) (EA 11 23)

Rubio G, Faculty of Medicine, Complutense University, Madrid, Spain

This research investigated how three psychophysiological processes in alcohol dependent patients are related to alcohol relapse. The three investigated processes include: attentional bias, the phenomenon whereby individuals find they are distracted by objects or information that is relevant to them (in this case: alcohol related stimuli); startle magnitude, the motivational response to alcohol, and; inhibitory control, where an individual inhibits their impulses or response to stimuli.

The results showed that alcohol dependent patients show more attentional bias compared to controls. Patients also had a lower startle magnitude than controls, meaning that they considered alcohol pictures more appetitive. Patients exhibited higher reaction times than controls for inhibiting GO-NoGO actions (a measure of inhibitory control). All three processes were associated with alcohol relapse. Overall, the best psychophysiological predictors for relapse were attentional bias and difficulty for inhibitory control. Moreover, inhibitory mechanisms appear to be more relevant than the motivational ones in order to explain relapses of alcohol dependent patients. Inhibitory mechanisms are involved in alcohol dependence and in the severity of alcohol dependence, but motivational response to alcohol cues is related to alcohol dependence.

Publications

Sion A, Jurado-Barba R, Alonso MJ and **Rubio-Valladolid G** (2017) Inhibitory capacity assessment in alcohol dependent patients: translation from a modified stop signal task. *Actas Espanolas de Psiquiatria*, 45(1):21-31

Marin M, **Rubio-Valladolid G**, Jurado R, Ponce G, Martinez I, Alvarez MJ and Moratti S (2014) EPA-0843 - Relationship between psychophysiological processes involved in alcohol dependence. *European Psychiatry*, 29(Supplement 2): S674

Neurobiological and behavioural consequences of adolescent alcohol consumption; studies of causal links between early-life conditions and vulnerability for alcohol use disorders (2011) (EA 11 30)

Nylander I, Department of Pharmaceutical Biosciences, Neuropharmacology, Addiction and Behaviour, University of Uppsala, Sweden

Adolescent drug exposure will affect the development of the brain and thereby cause changes in behaviour and in propensity for alcohol use disorders (AUD). This study investigated the impact of adolescent alcohol exposure on brain opioids, dopamine and brain function and also its interaction with early-life psychosocial stress versus no stress (maternal separation in an animal model).
The results showed that exposure to rearing conditions related to early-life stress or adolescent alcohol drinking change the behavioural development with regard to, for example, risk assessment behaviour and alter the response to alcohol later in life. In addition, adolescent voluntary drinking affects endogenous morphine-like substances in the brain and these effects are seen regardless of rearing in early-life protective/beneficial conditions or conditions related to early-life psychosocial stress. Results from these studies showed that the environmental influences in adolescence have a longstanding impact on the brain, on responses to alcohol and on the susceptibility for excessive alcohol consumption and AUD. Both the behavioural effects and the neurobiological effects are of interest since altered risk assessment behaviour and deranged opioid function in the brain has been associated with vulnerability for alcohol use disorders.

Publications

Todkar A, Granholm L, Aljumah M, Nilsson KW, Comasco E and **Nylander I** (2016) HPA axis gene expression and DNA methylation profiles in rats exposed to early life stress, adult voluntary ethanol drinking and single housing. *Frontiers in Molecular Neuroscience*, 8:90

Granholm L, Rowley S, Ellgren M, Segerström L and **Nylander I** (2015) Impact of adolescent ethanol exposure and adult amphetamine self-administration on evoked striatal dopamine release in male rats. *Psychopharmacology*, 232:4421-4431

Bendre M, Comasco E, **Nylander I** and Nilsson KW (2015) Effect of voluntary alcohol consumption on *Maoa* expression in the mesocorticolimbic brain of adult male rats previously exposed to prolonged maternal separation. *Translational Psychiatry,* 5(12): e690

Vrettou M, Granholm L, Todkar A, Nilsson KW, Wallén-Mackenzie Å, **Nylander I** and Comasco E (2015) Ethanol affects limbic and striatal presynaptic glutamatergic and DNA methylation gene expression in outbred rats exposed to early-life stress. *Addiction Biology*, 22(2):369-380

Palm S and **Nylander I** (2014) Dopamine release dynamics change during adolescence and after voluntary alcohol intake. *PLoS ONE*, 9(5): e96337

Palm S, Momeni S, Lundberg S, **Nylander I** and Roman E (2014) Risk-assessment and risk-taking behavior predict potassium- and amphetamine-induced dopamine release in the dorsal striatum of rats. *Frontiers in Behavioral Neuroscience*, 8:236

Palm S and **Nylander I** (2014) Alcohol-induced changes in opioid peptide levels in adolescent rats are dependent on housing conditions. *Alcohol: Clinical and Experimental Research*, 38(12):2978-2987

Daoura L, **Nylander I** and Roman E (2013) Qualitative differences in pup-retrieval strategies in a maternal separation paradigm. *Journal of Behavioral and Brain Science*, 3:603-616

Palm S, Daoura L, Roman E and **Nylander I** (2013) Effects of rearing conditions on behaviour and endogenous opioids in rats with alcohol access during adolescence. *PLoS ONE*, 8(10):e76591

Nylander I and Roman E (2013) Is the rodent maternal separation model a valid and effective model for studies on the early-life impact on ethanol consumption? *Psychopharmacology*, 229:555-569

Nylander I and Roman E (2012) Neuropeptides as mediators of the early-life impact on the brain; implications for alcohol disorders. *Frontiers in Molecular Neuroscience*, 5(77)

Theses and Awards

Dr. Loudin Daoura - PhD 2013, Early environment and adolescent ethanol consumption; Effects on endogenous opioids and behaviour in rats.

Dr. Sara Palm - PhD 2014, Early environment, adolescent alcohol drinking and neurobiological responses to drugs.

Profesor Nylander - ERAB Publications Award 2018

Identification of a genetic risk-factor for alcohol seeking and relapse (2011) (EA 11 35)

de Vries T, VU University, Amsterdam, The Netherlands

The main aim of the project was to prove that a genetically engineered level of impulsivity is a vulnerability factor for alcohol addiction.
The results showed that in mice, enhanced impulsivity coincides with increased motivation to take alcohol, as well as relapse vulnerability. Further studies are needed to determine whether impulsivity/inattention and alcohol seeking depend on common or separate molecular mechanisms.
The identification of the gene (Nrg3) that modulates the level of impulsivity and alcohol addiction related behaviour in mice provides a molecular entry into better understanding of alcohol addiction.

Publications

Loos M, Staal J, Smit AB, **de Vries TJ** and Spijker S (2013) Enhanced alcohol self-administration and reinstatement in a highly impulsive, inattentive recombinant inbred mouse strain. *Frontiers in Behavioral Neuroscience*, 7(article 151)

Images of adolescent alcohol use and health in Italy. A study of teenagers' drinking and societal reactions to it (2011) (EA 11 37)

Prina F, Department of Social Science, University of Turin, Italy

This study investigated the images of Italian adolescents and adults of adolescents' alcohol use. Results show how young people's images about drinking are quite traditional (as they have a negative attitude towards drunkenness - importance is given to conviviality of drinking) but also new elements have to be considered especially the rise of so-called pharmaceutical drinking. Adults' images of youth drinking diverge from those of young people. Particularly, adults overestimate young people's appreciation for drunkenness and at the same time they underestimate the pharmaceutical use of alcohol, aimed to face life's troubles or to enhance social performance. Moreover, adults understate young peoples' risk awareness and seem to be uncertain about what alcohol-specific

parenting practices are the best, as they perceive an ongoing change in young people's lifestyles.

This research provided new crucial insights to improve alcohol policies and set effective prevention strategies. Particularly:

- caring adults need more information about what kind of parenting practices related to alcohol are effective;
- there are gaps in the understanding of youth drinking between adults and young people;
- the growth of youth drinking in order to cope with troubles requires more attention;
- the effects of non-compliance with formal norms (first of all by adults) have to be valued; and
- a general reflection is needed about the dominance of moral panic spread by media about youth drinking and its effects.

Publications

Rolando S and Katainen A (2014) Images of alcoholism among adolescents in individualistic and collectivistic geographies. *Nordic Studies on Alcohol and Drugs*, 31:189-205

Rolando S, Beccaria F, Petrilli E and **Prina F** (2014) Adults' views of young people's drinking in Italy: an explorative qualitative research. *Drugs: Education, Prevention and Policy*, 21(5):388-397

Petrilli E, Beccaria F, **Prina F** and Rolando S (2014) Images of alcohol among Italian adolescents - Understanding their point of view. *Drugs: Education, Prevention and Policy*, 21(3):211-220

Dietary patterns and nutrient intakes of beer consumers compared to consumers of other (non-) alcoholic drinks (2011) (EA 11 45)

de Graaf K, Wageningen University, The Netherlands

A light to moderate intake of alcohol has been shown to have beneficial effects on coronary heart disease. Some studies show that this beneficial effect is stronger for specific alcoholic beverages, such as wine. Yet, it is not known whether wine itself is more beneficial compared to other alcoholic beverages, or whether dietary patterns and nutrient intakes play a role.

This research, based on observational studies, showed that consumption of beer, wine, and spirits is associated with specific dietary habits, e.g. a healthier diet for wine consumers and less healthy dietary habits for those with a beer preference. However, these differences in dietary habits were largely – if not completely – explained by socio-demographic and lifestyle factors. Hence, the different health effects of beer, wine, and spirits are probably caused by the underlying differences in socio-demographics and lifestyle of the study population.

Therefore, it seems that alcoholic beverage preference may not be independently related to diet and health status but is merely a proxy for socio-demographic and lifestyle factors. It is important to keep all these factors in mind when studying the effects of beer, wine, and spirits on health.

Publications

Sluik D, Jankovic N, Hughes M, O'Doherty MG, Schöttker B, Drygas W, Rolandsson O, Männistö S, Ordóñez-Mena JM, Ferriere J, Bamia C, de Gaetano G, Kiefte-De Jong JC, Franco OH, Sluijs I, Spijkerman AMW, Sans S, Eriksson S, Kromhout D, Trichopoulou A, Wilsgaard T, Brenner H, Kuulasmaa K, Laatikainen T, Söderberg S, Iacoviello L, Boffetta P, Kee F and Feskens EJM (**Dr. de Graaf's team**) (2017) Alcoholic beverage preference and diabetes incidence across Europe: the Consortium on Health and Ageing Network of Cohorts in Europe and the United States (CHANCES) project. *European Journal of Clinical Nutrition*, 71:659–668

Sluik D, Jankovic N, O'Doherty MG, Geelen A, Schöttker B, Rolandsson O, Kiefte - de Jong JC, Ferrieres J, Bamia C, Fransen HP, Boer JMA, Eriksson S, Martinez B, Huerta JM, Kromhout D, de Groot LCPGM, Franco OH, Trichopoulou A, Boffetta P, Kee F and Feskens EJM (**Dr. de Graaf's team**) (2016) Alcoholic beverage preference and dietary habits in elderly across Europe: analyses within the consortium on health and ageing: network of cohorts in Europe and the United States (CHANCES) project. *PLoS ONE*, 11(8): e0161603

Sluik D, Brouwer-Brolsma EM, de Vries JHM, Geelen A and Feskens EJM (**Dr. de Graaf's team**) (2016) Associations of alcoholic beverage preference with cardiometabolic and lifestyle factors: the NQplus study. *BMJ open*, 6(6):e010437

Sluik D, Bezemer R, Sierksma A and Feskens EJM (**Dr. de Graaf's team**) (2016) Alcoholic beverage preference and dietary habits: a systematic literature review. *Critical Reviews in Food Science and Nutrition*, 56(14):2370-2382

Sluik D, van Lee L, Geelen A and Feskens EJM (**Dr. de Graaf's team**) (2014) Alcoholic beverage preference and diet in a representative Dutch population: the Dutch National Food consumption Survey 2007 – 2010. *European Journal of Clinical Nutrition*, 68(3):287-94; doi:10.1038/ejcn.2013.279

Sluik D, van Lee L, Geelen A and Feskens EJM (**Dr. de Graaf's team**) (2013) Alcoholic beverage preference and diet in the Netherlands. *Annals of Nutrition and Metabolism*, 63(suppl1): 957

The pathway of early life social economic status to midlife alcohol use to later life ill health (2012) (EA 12 06)

Yang M, University of Nottingham, UK

This research focused on the complex and indirect relationships between socio-economic status (SES), alcohol consumption and health problems using a life-course approach. It attempted to throw light on the pathway of early life SES to midlife alcohol use and then to later life health outcomes, with particular reference to health inequalities. To investigate this, 50 years of data from the 1958 British National Birth Cohort study were used.

The main findings were that those with parents in a low socioeconomic status (PSES) are more likely to report worse health outcomes at age 50 compared to the higher PSES trajectory groups and this association is moderated by different levels of midlife alcohol consumption for both men and women. The bottom PSES trajectory group are more likely to consume less alcohol throughout the 27-year period compared to the higher PSES trajectory groups.

At age 23, the bottom PSES group drank more beer on a weekly basis, whereas the top 25% PSES group drank more wine.

Significant risk factors for alcohol consumption included:- getting into trouble with the police at age 16; being more aggressive; the teacher's views of the parents being overly interested in the child's education; drinking more alcohol and spending more money on alcohol at age 16. Significant protective factors included white ethnicity and weekly outings with parents at age 11.

Female cohort members' midlife drinking was shown to have a more direct impact on the later life health outcomes at age 50 compared to the men.

This research provided information that can help target health promotion messages that are appropriate to different groups of people (men and women; different socioeconomic groups), at different times across the lifespan, and for different beverages (beer versus wine). Furthermore, early risk and protective factors have been identified, and these can be addressed in schools and family health initiatives.

Publications

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The effects of psychosocial factors upon risk of developing alcohol use disorders. A longitudinal study (2012) (EA 12 10)

Flensborg-Madsen T, Institute of Public Health, University of Copenhagen, Denmark

The purpose of this study was to investigate, in two large Danish prospective studies, whether quality of life and social network were associated with the later risk of being admitted to a hospital and receive a diagnosis of alcohol use disorder (AUD). There were two hypotheses. The first was that people's overall evaluation of their quality of life/vital exhaustion (an emotional state characterized by fatigue and depressive symptoms) is a strong predictor of (AUD) risk. The second was that social network is a predictor of later development of AUD and that the content i.e. the qualitative experience of one's network, is especially important to prevent excess alcohol drinking and thereby the possible development of AUD.

The results of a first study showed that living alone and not being married or cohabiting with a partner were predictors of developing AUD among men. Further, frequent contact with friends was associated with higher risk of AUD among both sexes.

A second study found that vital exhaustion was significantly associated with higher risk of AUD in both men and women. Hence, for both genders, the risk of AUD increased dose-dependently with increasing vital exhaustion. Individuals who reported a high vital exhaustion score had a 2- to 3-fold risk of AUD in both men and women.

A third study showed that the accumulation of life events in childhood, adulthood and work life was not associated with increased risk of AUD. A higher risk of AUD was, however, indicated in men and women suffering serious economic problems, and in women being placed in care outside of the home during childhood.

It was concluded that several psychosocial factors have an influence upon the risk of developing AUD. This increased the understanding of potential risk factors in the development of AUD and thereby increased the basis on which future intervention programs can be built.

Publications

Just-Østergaard E, Mortensen EL, Tolstrup J and **Flensborg-Madsen T** (2018) Vital exhaustion and risk of alcohol use disorders: a prospective cohort study. Journal of Psychosomatic Research, 114:25-30

Just-Østergaard E, Mortensen EL and **Flensborg-Madsen T** (2018) Major life events and risk of alcohol use disorders: a prospective cohort study. *Addiction*, 113(1):25-33

Mikkelsen SS, Tolstrup JS, Becker U, Mortensen EL and **Flensborg-Madsen T** (2015) Social network as predictor of onset of alcohol use disorders: A prospective cohort study. *Comprehensive Psychiatry*, 61:57-63

Neutrophil function in acute alcoholic hepatitis and alcohol-induced liver toxicity utilising a novel in vitro model of acute liver injury (2012) (EA 12 13)

Shawcross D L, Institute of Liver Study, King's College, London, UK

Sepsis and resultant organ failure are frequently the cause of death in patients with acute alcoholic hepatitis. This research investigated the defective pathways of the immune system's response to infection in alcohol-induced liver injury. Neutrophils (a type of white blood cell) play a key role in hepatocellular damage and susceptibility to infection. The underlying mechanism is however poorly understood. Data from this study showed that in patients with acute alcoholic hepatitis, neutrophils demonstrate reduced expression of receptors that play a role in the immune system. Additionally, neutrophils fail to appropriately up-regulate these receptors in response to bacteria. Overall, results showed impaired neutrophil response to bacterial stimulus in alcohol-related liver injury which could lead to increased susceptibility to infection.

Publications

Tranah TH, Vijay GKM, Ryan JM, Abeles RD, Middleton PK and **Shawcross DL** (2017) Dysfunctional neutrophil effector organelle mobilization and microbicidal protein release in alcohol-related cirrhosis. *American Journal of Physiology. Gastrointestinal and Liver Physiology,* 313(3):G203-G211

Markwick LJ, Riva A, Ryan JM, Cooksley H, Palma E, Tranah TH, Manakkat Vijay GK, Vergis N, Thursz M, Evans A, Wright G, Tarff S, O'Grady J, Williams R, **Shawcross DL** and Chokshi S (2015) Blockade of PD1 and TIM3 restores innate and adaptive immunity in patients with acute alcoholic hepatitis. *Gastroenterology*, 148(3):590-602

Taylor NJ, Manakkat GK, Abeles RD, Auzinger G, Bernal W, Ma Y, Wendon A and **Shawcross DL** (2014) The severity of circulating neutrophil dysfunction in

patients with cirrhosis is associated with 90-day and 1-year mortality. *Alimentary Pharmacology & Therapeutics*, 40:705-715

Brain and plasma epigenetic markers for alcohol addiction and its cognitive deficits (2012) (EA 12 21)

López-Moreno JA, Department of Psychobiology, Faculty of Psychology, Complutense University, Madrid, Spain

The aim of this study was to investigate the association between epigenetic gene expression in brain and plasma under several operant alcohol self-administration procedures.

The results demonstrated that histone deacetylases, are dysregulated after the consumption of alcohol. During the first exposures to alcohol, the expression of histone deacetylases is reduced; however, when the individual repeatedly uses alcohol the expression of histone deacetylases is normalized or in most cases, increased. This has been proved in blood samples using humans and rats. In addition, one study focused on the effects of a pharmacological treatment (topiramate) in the context of the dual dependence of alcohol and cocaine in pre-clinical research (using animal models). Unlike naltrexone, another pharmacological treatment approved for the treatment of alcoholism, topiramate was able to prevent the increase of alcohol intake induced by the administration of cocaine. This study showed that these effects were associated with changes in gene expression (e.g., histone deacetylases) in the prefrontal cortex, a brain region that is key in the control and regulation of behaviour.

The results of another study proved that a specific mutation in the gene encoding for one enzyme that metabolizes the endocannabinoids (C385A CC *FAAH)*, such as anadamide, was associated with risky alcohol consumption. This finding was replicated in two independent samples of individuals suggesting that this specific gene mutation would be useful in developing early markers for individuals who are at higher risk for alcohol problems. More recently, another two studies on this topic have been completed. The first one investigated the effects of one of the most commonly consumed energy drinks worldwide, i.e. Red Bull, on alcohol consumption. One key finding was that the effects of Red Bull on alcohol self-administration depended on the concentration: the higher the concentration of alcohol in the mix, the higher the amount of alcohol consumption. Therefore, Red Bull might be a vulnerability factor to develop alcoholism given that it intensifies the consumption of higher concentrations of

alcohol. The second study examined the interaction between hypothyroidism and alcohol consumption. Hypothyroidism increased the voluntary consumption of alcohol and this was enhanced by thyroid hormone supplementation. These last results suggest that hypothyroid patients would need more personalized attention in terms of ethanol consumption and the usefulness of embracing the thyroid axis in the study of alcohol addiction, including as a possible therapeutic target for the treatment of alcoholism and its comorbid disorders.

These findings have helped to unravel the role of the expression of epigenetic genes in alcohol addiction and its cognitive deficits and discovered novel central and peripheral epigenetic markers for alcohol addiction.

Publications

Echeverry-Alzate V, Bühler KM, Calleja-Conde J, Huertas E, Maldonado R, Rodríguez de Fonseca R, Santiago C, Gómez-Gallego F, Santos A, Giné E and **López-Moreno JA** (2019) Adult-onset hypothyroidism increases ethanol consumption. *Psychopharmacology*, 236(4):1187–1197

Roldán M, Echeverry-Alzate V, Bühhler KM, Sánchez-Diez IJ, Calleja-Conde J, Olmos P, Boehm SL, Maldonado R, Rodríguez de Fonseca F, Santiago C, Gómez-Gallego F, Giné E and **López-Moreno JA** (2018). Red Bull® energy drink increases consumption of higher concentrations of alcohol. *Addiction Biology*, 23(5):1094-1105

López-Moreno JA, Marcos M, Calleja-Conde J, Echeverry-Alzate V, Bühler KM, Costa-Alba P, Bernardo E, Laso F-J, de Fonseca FR, Nadal R, Paz Viveros M, Maldonado R and Giné E (2015) Histone deacetylase gene expression following binge alcohol consumption in rats and humans. *Alcoholism: Clinical and Experimental Research*, 39(10):1939-1950

Penasco S, Mela V, **López-Moreno JA**, Viveros MP and Marco EM (2015) Early maternal deprivation enhances voluntary alcohol intake induced by exposure to stressful events later in life. *Neural Plasticity*, Volume 2015

Bühler KM, Giné E, Echeverry-Alzate V, Calleja-Conde J, Rodriguez de Fonseca F and **López-Moreno J** (2015) Common single nucleotide variants underlying drug addiction: more than a decade of research. *Addiction Biology*, 20(5):845-871

Echeverry-Alzate V, Giné E, Bühler K-M, Calleja-Conde J, Olmos P, Gorriti MA, Nadal R, Rodriguez de Fonseca F and **López-Moreno JA** (2014) Effects of topiramate on ethanol-cocaine interactions and DNA methyltransferase gene expression in the rat prefrontal cortex. *British Journal of Pharmacology*, 171(12):3023-3036

Bühler K-M, Huertas E, Echeverry-Alzate V, Giné E, Molto E, Montoliu L and **López-Moreno JA** (2014) Risky alcohol consumption in young people is associates with the fatty acid amide hydrolase gene polymorphism C385A and affective rating of drug pictures. *Molecular Genetics and Genomics*, 289(3):279-89

Theses and Awards

Professor López-Moreno - ERAB Publications Award 2019

The consequences of binge-drinking on learning and memory. How does it work in the brain? (2012) (EA 12 28)

Pierrefiche O, Faculty of Pharmacy, University of Picardie Jules Verne, Amiens, France

Binge drinking is common in adolescents, but the impact of only a few binges on learning and memory appears underestimated. Many studies have tested the effects of long and intermittent ethanol exposure on long-term synaptic potentiation, and whether long-term synaptic depression is affected remains unknown. This project investigated in adolescent rats the effects of a few binges of ethanol on synaptic plasticity, the cellular mechanisms of learning and memory and on rat's memory performance. The results showed that two binges only, can induce cognitive deficits that remain up to two days after elimination of ethanol. This demonstrates that even a relatively low amount of alcohol is detrimental to cognitive function and that the negative effects on memory performance last for a long period after ethanol elimination from the body.

Publications

Silvestre de Ferron B, Bennouar K-E, Kervern M, Alaux-Cantin S, Robert A, Rabiant K, Antol J, Naassila M and **Pierrefiche O** (2015) Two binges of ethanol a day keep the memory away in adolescent rats: key role for GLUN2B subunit. *International Journal of Neuropsychopharmacology*, 19(1)

More effective change of alcohol-related cognitive biases via enhancement of mediating processes (2012) (EA 12 39)

Gladwin T, University of Amsterdam, The Netherlands

New treatments have been developed for alcohol addiction, but the most effective ways to help patients still need to be determined. This research focused on improving the ability to treat patients with alcohol dependence using novel techniques involving the stimulation of the brain to enhance learning. The results suggested that transcranial Direct Current Stimulation (tDCS) can reduce craving

and relapse rates, in particular in combination with approach-avoidance training. More research and clinical interventions on the combination of tDCS and Cognitive Bias Modification are needed to confirm these results and to further explore novel intervention methods.

Publications

Den Uyl TE, **Gladwin TE**, Lindenmeyer J and Wiers RW (2018) A clinical trial with combined transcranial Direct Current Stimulation and attentional bias modification in alcohol dependent patients. *Alcoholism: Clinical and Experimental Research*, 22(6):1632-1640

Gladwin TE, Salemink E, Garritsen H, Noom S, Kraaij G and Wiers RW (2018) Is alcohol-related aggression related to automatic alcohol-power or alcohol-aggression associations? *Psychology of Violence*, 8(2):229-237

Gladwin TE (2017) Negative effects of an alternating-bias training aimed at attentional flexibility: A single session study. *Health Psychology and Behavioral Medicine*, 5(1): 41-56

Gladwin TE (2017) Attentional bias variability and cued attentional bias for alcohol stimuli. *Addiction Research and Theory*, 25 (1):32-38

Den Uyl TE, **Gladwin TE**, Rinck M, Lindenmeyer J and Wiers RW (2016) A Clinical Trial with Combined Transcranial Direct Current Stimulation and Alcohol Approach Bias Retraining. *Addiction Biology*, 22(6):1632-1640

Korucuoglu O, **Gladwin TE**, Baas F, Mocking RJT, Ruhe HG, Groot PFC and Wiers RW (2016) Neural response to alcohol taste cues in youth: effects of the OPRM1 gene. *Addiction Biology*, 22(6):1562-1575

Wiers CE, **Gladwin TE**, Ludwig VU, Gropper S, Stuke H, Wiers RW, Walter H and Bermpohl F (2016) Comparing three cognitive biases for alcohol cues in alcohol dependence. *Alcohol and Alcoholism*, 52(2):242–248

Den Uyl TE, **Gladwin TE** and Wiers RW (2016) Electrophysiological and Behavioural Effects of Combined Transcranial Direct Current Stimulation and Alcohol Approach Bias Retraining in Hazardous Drinkers. *Alcoholism: Clinical and Experimental Research*, 40(10):2124-2133

Korucuoglu O, **Gladwin TE** and Wiers RW (2016) The effect of acute alcohol on motor-related EEG asymmetries during preparation of approach or avoid alcohol responses. *Biological Psychology,* 114:81-92

Wiers RW, Boelema S, Nikolaou K and **Gladwin TE** (2015) On the Development of Implicit and Control Processes in Relation to Substance Use in Adolescence. *Current Addiction Reports* 2(2):141-155

Wiers CE, Stelzel C, **Gladwin TE**, Park SQ, Pawelczack S, Gawron CK, Stuke H, Heinz A, Wiers RW, Rinck M, Lindenmeyer J, Walter H and Bermpohl F (2015) Effects of Cognitive Bias Modification-Training on Neural Alcohol Cue Reactivity in Alcohol-Dependence. *American Journal of Psychiatry*, 172(4):335-343

Korucuoglu O, **Gladwin TE** and Wiers RW (2015) Alcohol-induced changes in conflict monitoring and error detection as predictors of alcohol use in late adolescence. *Neuropsychopharmacology*, 40(3):614-21

Den Uyl TE, **Gladwin TE** and Wiers RW (2015) Transcranial Direct Current Stimulation, Implicit Alcohol Associations and Craving. *Biological Psychology*, 105:37-42

Gladwin TE, Rinck M, Eberl C, Becker ES, Lindenmeyer J and Wiers RW (2014) Mediation of Cognitive Bias Modification for Alcohol Addiction via Stimulus-specific Alcohol Avoidance Association. *Alcoholism: Clinical and Experimental Research*, 39(1):101-107

Gladwin TE, Mohr SE and Wiers RW (2014) The Potential Role of Temporal Dynamics in Approach Biases: Delay-dependence of a General Approach Bias in an Alcohol Approach-Avoidance Task. *Frontiers in Psychology,* 5:1398

Theses and Awards

Professor Gladwin - ERAB Publications Award 2018

Life Course Study of Alcohol Harm in Three Generations: the Importance of Individual and Contextual Factors (2013) (EA 13 05)

Sidorchuk A, Department of Public Health Science, Karolinska Institute, Stockholm, Sweden

The main aim of this study was to establish and study an intergenerational patterning of alcohol use and its medical, psychological and social consequences in a life course perspective of three generations of Swedish people by modelling the trajectories for individuals following a distinct outline of change of alcohol use over age (within generations) and time (between generations).

The results highlighted that those granddaughters and grandsons from socially disadvantaged families have different risks in developing alcohol-related problems. Also, association between familial history of social hardship and grandchildren's alcohol-related disorders seem to become weaker with time. In contrast, parental social adversity impacts the development of alcohol-related disorders in males, but not in females regardless of time period.

The role of grandparental social class in developing alcohol-related disorders in grandchildren appears to decline over time; however, if social adversity persists in families and both grandparents and parents belong to disadvantaged social class it increases the risk of developing alcohol- attributable problems among males.

Publications

Sidorchuk A, Goodman A and Koupil I (2018) Social class, social mobility and alcohol-related disorders in Swedish men and women: A study of four generations. *PLoS ONE,* 13(2): e0191855

Sidorchuk A, Goodman A and Koupil I (2016) Social class, social mobility and alcohol-related disorders in four generations of Swedish families: Anna Sidorchuk, *European Journal of Public Health*, 26, Issue suppl 1 ckw167.022

Is the neuroimmune response involved in the neurotoxic and behavioural consequences of binge alcohol drinking during adolescence? (2013) (EA 13 08)

Guerri C, Cell Pathology Laboratory, Research Center Prince Felipe, Valencia, Spain

Studies have demonstrated the vulnerability of the adolescent brain to actions of ethanol and the long-term consequences of binge drinking, including the behavioural and cognitive deficits that result from alcohol neurotoxicity, and increased risk of alcohol abuse and dependence. The aim of this research was to assess whether ethanol treatment in adolescence promotes the long-term synaptic and molecular events associated with alcohol abuse and addiction. Using adolescent mice, the results demonstrated that the neuroimmune response is involved in the neurotoxic and behavioural consequences of binge alcohol drinking during adolescence.

The project also showed some gender differences in the inflammatory cytokine and chemokine profiles induced by binge ethanol drinking in adolescence. Thus, using plasma of male and female adolescents and young adults during acute alcohol intoxication, it was shown that alcohol intoxication increased the plasma levels of several cytokine and chemokine [interferon-γ, interleukin (IL)-10, IL-17A, IL-1β, IL-2, IL-4, IL-6, IL-8, fractalkine, monocyte chemoattractant protein 1 (MCP-1) and macrophage inflammatory protein 1α (MIP-1α)] and upregulated TLR4 mRNA levels in females, while elevation of colony-stimulating factor was only observed in the plasma of males. In wild-type female adolescent mice, intermittent ethanol treatment increased the levels of several cytokines (IL-17A and IL-1β) and chemokines (MCP-1, MIP-1α and fractalkine) in PFC and in serum (IL-17A, MCP-1 and MIP-1α), but significant differences in the fractalkine levels in PFC were observed only in male mice. No changes in serum or prefrontal cortex

cytokine and chemokine levels were noted in ethanol-treated male or female TLR4-knockout mice. The findings revealed that females are more vulnerable than males to inflammatory effects of binge ethanol drinking and suggested that TLR4 is an important target of ethanol-induced inflammation and neuroinflammation in adolescence.

The results highlighted a new role of the neuroimmune function in alcohol consumption and addiction and open up new avenues to develop pharmacological treatments that can normalize the immune signaling responsible for long-term effects in adolescence.

Publications

Pascual M, Montesinos J and **Guerri C** (2018) Role of the innate immune system in the neuropathological consequences induced by adolescent binge drinking. *Journal of Neuroscience Research*, 96(5):765-780

Pascual M, Montesinos J, Marcos M, Torres JL, Costa Alba P, García García F, Laso FJ and **Guerri C** (2017) Gender differences in the inflammatory cytokine and chemokine profiles induced by binge ethanol drinking in adolescence. *Addiction Biology*, 22(6):1829-1841

Montesinos J, Gil A and **Guerri C** (2017) Nalmefene Prevents Alcohol-Induced Neuroinflammation and Alcohol Drinking Preference in Adolescent Female Mice: Role of TLR4. *Alcoholism: Clinical and Experimental Research*, 41(7),1257-1270

Montesinos J, Pascual M, Rodríguez-Arias M, Miñarro J and **Guerri C** (2016) Involvement of TLR4 in the long-term epigenetic changes, rewarding and anxiety effects induced by intermittent ethanol treatment in adolescence. *Brain, Behavior and Immunity*, 53:159-171

Alfonso-Loeches S, Urena-Peralta J, Morillo-Bargues J, Gomez-Pinedo U and **Guerri C** (2015) Ethanol-induced TLR4/NLRP3 neuroinflammatory response in microglial cells promotes leukocyte infiltration across the BBB. *Neurochemical Research*, 41(1-2):193-209

Montesinos J, Pascual M, Pla A, Maldonado C, Rodriguez-Arias M, Minarro J and **Guerri C** (2015) TLR4 elimination prevents synaptic and myelin alterations and long-term cognitive dysfunctions in adolescent mice with intermittent ethanol treatment. *Brain, Behavior, and Immunity*, 45:233-244

Alfonso-Loeches S, Urena-Peralta JR, Morillo-Bargues MJ, Oliver-De la Cruz J and **Guerri C** (2014) Role of mitochondria ROS generation in ethanol-induced NLRP3 inflammasome activation and cell death in astroglial cells. *Frontiers in Cellular Neuroscience*, 8(216)

Pascual M, Balino P, Aragon CMG and **Guerri C** (2014) Cytokines and chemokines as biomarkers of ethanol-induced neuroinflammation and anxiety-related behaviour: role of TLR4 and TLR2. *Neuropharmacology*, 89:352-359

Impact of alcohol consumption on the athero-protective process of the reverse cholesterol transport (2013) (EA 13 09)

Zanotti I, Università degli Studi di Parma, Parma, Italy

Reverse cholesterol transport (RCT) may be one of the mechanisms accounting for positive effects of alcohol consumption on cardiovascular health. This study investigated the effects of moderate and excess alcohol consumption on RCT.
The results showed that moderate alcohol consumption slightly promoted the first steps of RCT in vivo, at least in part by up-regulating the expression of scavenger receptor class B type I (SR-BI) in the liver. Conversely, moderate/binge alcohol consumption seems not to significantly impair the process. In addition, moderate/binge alcohol ingestion caused a deleterious modification of lipoprotein plasma profile, leading to a significant increase of total and LDL- cholesterol. Interestingly, although a concurrent raise of HDL was observed, these lipoproteins were demonstrated to have impaired antiatherogenic functions, as revealed by their reduced capacity to promote cholesterol efflux. It is important to notice that no toxic effects related to these levels of alcohol consumption were evident, as measured by hepatic function.
Moderate alcohol consumption is likely to slightly promote the first steps of RCT, thus exerting potential athero-protective activity. Moderate/binge alcohol consumption, despite devoid of hepatic toxic effects, seems to negatively affect lipoprotein profile and function.
These findings are useful to define nutritional guidelines and perform interventions for subjects with risky drinking behaviour.

Publications

Greco D, Battista S, Mele L, Piemontese A, Papotti B, Cavazzini S, Potì F, Di Rocco G, Poli A, Bernini F and **Zanotti I** (2018) Alcohol Pattern Consumption Differently Affects the Efficiency of Macrophage Reverse Cholesterol Transport in Vivo. *Nutrients*, 10:1885; doi: 10.3390/nu10121885.

Synthesis and pharmacological characterization of novel positive allosteric modulators of the $GABA_B$ receptor: focus on their "anti- alcohol" potential (2013) (EA 13 20)

Maccioni P, Neuroscience Institute, National Research Council of Italy, Cagliari, Italy

$GABA_B$ receptors are classified as inhibitory receptors as they reduce the release of neurotransmitter. They are located in the central nervous system and are involved in several behavioural actions of ethanol. This research was designed to synthesize and pharmacologically characterize new positive allosteric modulators (PAMs) of the $GABA_B$ receptor with "anti-alcohol" potential. PAMs are molecules that can increase the activity of $GABA_B$ receptors. The results demonstrated that a newly synthesized $GABA_B$ PAM, named COR659, was potent and effective in reducing oral alcohol self-administration and reinstatement of alcohol seeking in alcohol-preferring rats. Insights in the "anti-alcohol" profile of COR659 as well as known $GABA_B$ PAMs strengthened the hypothesis that they may also represent a new, potentially effective therapeutic option for alcohol use disorder.

Publications

Maccioni P, Colombo G, Lorrai I, Fara F, Carai MAM, Gessa GL, Brizzi A, Mugnaini C and Corelli F (2019) Anti-addictive properties of COR659 – Additional pharmacological evidence and comparison with a series of novel analogues. *Alcohol*, 75:55-66

Maccioni P, Fara F, Lorrai I, Acciaro A, Mugnaini C, Corelli F and Colombo G (2019) Suppressing effect of CMPPE, a new positive allosteric modulator of the $GABA_B$ receptor, on alcohol self-administration and reinstatement of alcohol seeking in rats. *Alcohol*, 75:79-87

Maccioni P, Lorrai I, Contini A, Leite-Morris K and Colombo G (2017) Microinjection of baclofen and CGP7930 into the ventral tegmental area suppresses alcohol self-administration in alcohol-preferring rats. *Neuropharmacology.*136(A):146-158

Maccioni P, Colombo G, Lorrai I, Zaru A, Contini A, Carai MA, Gessa GL, Brizzi A, Mugnaini C and Corelli F (2017) Suppressing effect of COR659on alcohol, sucrose, and chocolate self-administration in rats: involvement of the $GABA_B$ and cannabinoid CB_1 receptors. *Psychopharmacology*, 234:2525–2543

Porcu A, Lobina C, Giunta D, Solinas M, Mugnaini C and Castelli MP (2016) In *vitro* and in vivo pharmacological characterization of SSD114, a novel $GABA_B$ positive allosteric modulator. *European Journal of Pharmacology*, 27(791):115-123

Colombo G, Lobina C, **Maccioni P**, Carai MAM, Lorrai I, Zaru A, Contini A, Mugnaini C, Corelli F and Gessa GL (2015) Anxiety-like behaviors at the end of the nocturnal period in sP rats with a "history" of unpredictable, limited access to alcohol. *Alcohol*, 49:707-712

Maccioni P, Vargiolu D, Thomas AW, Malherbe P, Mugnaini C, Corelli F, Leite-Morris KA, Gessa GL and Colombo G (2015) Inhibition of alcohol self-administration by positive allosteric modulators of the $GABA_B$ receptor in rats: lack of tolerance and potentiation of baclofen. *Psychopharmacology*, 232(10):1831-1841

Theses and Awards

Dr. Maccioni - ERAB Publications Award 2019

Risk and benefits of the ethanol and polyphenol content in beer: effects of moderate consumption on cardiovascular system (2013) (EA 13 24)

Lamuela-Raventós RM, University of Barcelona, Spain

Moderate alcohol consumption is associated with a decrease in cardiovascular risk, but fermented beverages seem to confer greater cardiovascular protection due to their polyphenolic content. Circulating endothelial progenitor cells (EPC) are bone-marrow-derived stem cells with the ability to repair and maintain endothelial integrity and function and are considered as a surrogate marker of vascular function and cumulative cardiovascular risk. This was the first study to investigate the effects of moderate beer consumption on the number of circulating EPC in high cardiovascular risk patients.

It found that the non-alcoholic fraction of beer increased the number of circulating EPC and the phenolic content of beer reduced leukocyte adhesion molecules and inflammatory biomarkers. The alcohol mainly improves the lipid profile and reduces some plasma inflammatory biomarkers related to atherosclerosis. Moderate beer consumption did not affect body weight and other anthropometric parameters.

In addition to this intervention study the possible risks and benefits of moderate beer consumption on hard endpoints related to cardiovascular disease (stroke, myocardial infarction or cardiovascular death) and any-cause mortality were evaluated using data from the PREDIMED study. Low and low-to-moderate consumption of beer was statistically and inversely associated with any-cause mortality. In addition, low and low-to-moderate beer consumption was statically significantly associated with a lower incidence of cardiovascular events.

These findings suggested that moderate beer consumption may decrease the risk of developing cardiovascular diseases by reducing adhesion molecules and inflammatory responses related to atherosclerosis, which may reduce the incidence of cardiovascular events risk and any-cause mortality.

Publications

Vilahur G, Casani L, Mendieta G, **Lamuela-Raventós RM**, Estruch R and Badimon L (2014) Beer elicits vasculoprotective effects through Akt/eNOS activation. *European Journal of Clinical Investigation*, 44:1177-1188

Chiva-Blanch G, Condines X, Magraner E, Roth I, Valderas-Martinez P, Arranz S, Casas R, Martinez-Huélamo M, Vallverdu-Queralt A, Quifer-Rada P, **Lamuela-Raventós RM**, and Estruch R (2014) The non-alcoholic fraction of beer increases stromal cell derived factor 1 and the number of circulating endothelial progenitor cells in high cardiovascular risk subjects: a randomized clinical trial. *Atherosclerosis*, 233(2):518-524

European Survey of University Student Alcohol Use (2013) (EA 13 48)

Cooke R, Aston University, UK

There is a need to understand the variability of patterns and predictors of drinking alcohol across Europe on this population, and this project provided an important contribution by mapping the patterns of alcohol consumption in European university students in six European countries – Denmark, England, Germany, Italy, Portugal, and Switzerland.

University students tend to favour heavy alcohol consumption, and as a result, increase their chances of suffering health and social problems. The single most important finding to emerge from this study was the considerable cross-group variability which occurred, not only in the patterns of drinking behaviour on university students which were displayed, but also in the social and psychological variables, such as sex-role egalitarianism or drinking motives.

A practical output from the project was the development of a standardized questionnaire validated for use in at least six European countries. It is worth noticing that collecting information on alcohol consumption in several European countries, using the same set of measures, allows for a clearer understanding of which factors are important in different countries.

As alcohol consumption among university students is a Europe-wide concern, policies and interventions on university students' alcohol consumption need to take cultural variability into account.

Publications

Fernandes-Jesus M, Beccaria F, Demant J, Fleig L, Menezes I, Scholz U, de Visser R and **Cooke R** (2016) Validation of the drinking motives questionnaire - revised in six European countries. *Addictive Behaviors*, 62:91-98

Theses and Awards

Dr. Cooke - ERAB Travel Award 2006/7/9.

The effect of alcohol on the absorption and toxicity of food chemicals via the gut (2014) (EA 14 02)

Wright M, Institute Cellular Medicine, Newcastle University, UK

This mouse study investigated whether alcohol consumption results in an increased uptake of food chemicals and if so, whether that increased uptake of food chemicals on a background of increased liver inflammation (due to gut leakiness to endotoxin) results in increased liver injury and fibrosis.
The data suggested that high level chronic exposure to alcohol does not result in an increased oral uptake of the food chemical tartrazine in a mouse model or to increased liver inflammation, liver injury or fibrosis.

Publications

Meyer SK, Probert PME, Lakey AF, Axon AR, Leitch AC, Williams FM, Jowsey PA, Blain PG, Kass GEN and **Wright MC** (2017) Hepatic effects of tartrazine (E 102) after systemic exposure are independent of oestrogen receptor interactions in the mouse. *Toxicology Letters*, 273:55–68

Study abroad students' drinking behaviour: a mixed methods longitudinal study on social norms and sojourner adjustment (2014) (EA 14 11)

Aresi G, Università Cattolica del Sacro Cuore, Italy

Young adults' alcohol consumption, substance use and unprotected sexual behaviour represent relevant public health concerns. Theories related to other travelling populations (i.e., tourists, spring breakers, sojourners and immigrants) and research on non-European study abroad students suggest that abroad students may be at greater risk for excessive alcohol consumption, drug use and unprotected casual sex. This first European study examined alcohol consumption and related negative outcomes, drug use and unprotected sexual behaviour in study abroad students (i.e., Erasmus). Students' behaviour was longitudinally assessed before departure, while abroad and once returned to their home countries. Participants (N = 906) increased the amount of alcohol consumed and experienced more alcohol-related consequences during the study abroad experience, though levels fell to below pre-departure levels when students returned home. Pre-departure expectations about alcohol use during the study abroad experience, psychological adjustment to the host country, lower academic involvement, and host country living costs were related to greater alcohol consumption while abroad. No statistically meaningful change in illicit drug use and unprotected sexual behaviour was observed, suggesting that the study abroad experience is dominated by alcohol. Studying abroad exposes European students to additional time-limited alcohol-related health risks, though riskier habits do not continue upon return.

Findings from this study have important public health implications and different entities (e.g., policy makers, international offices, health professionals in counselling service, student associations) operating in host and home institutions may consider intervening with reference to relevant risk factors.

Publications

Aresi G, Moore SC and Marta E (2021) The health behaviours of European study abroad students sampled from forty-two countries: Data from a three-wave longitudinal study. *Data in Brief,* 38:107285

Aresi G, Sorgente A, Moore SC and Marta E (2021) Analysing change among study abroad students. A novel application of the person-centred approach to alcohol use patterns. *International Journal of Intercultural Relations,* 82:220-231. doi.org/10.1016/j.ijintrel.2021.04.006

Aresi G, Moore S, Berridge D and Marta E (2019) A longitudinal study of European students' alcohol use and related behaviours as they travel abroad to study. *Substance Use and Misuse*, 54(7):1167-1177

Aresi G, Alfieri S, Lanz M, Marta E and Moore S (2018) Development and validation in five languages of a Multidimensional Motivations to Study Abroad Scale (MMSAS) among European Credit Mobility Students. *International Journal of Intercultural Relations*, 63:128-134

Aresi G, Moore S and Marta E (2016) Drinking, drug use and related consequences among university students completing study abroad experiences: A systematic review. *Substance Use and Misuse*, 51(14):1888-1904

Aresi G, Fattori F, Pozzi M and Moore S (2016) I am going to make the most out of it! Italian university Credit Mobility Students' Social Representations of alcohol use during study abroad experiences. *Journal of Health Psychology*, 1:1-10

Aresi G, Moore S and Marta E (2016) Italian credit mobility students significantly increase their alcohol intake, risky drinking and related consequences during the study abroad experience. *Alcohol and Alcoholism*, 51(6):723–726

Theses and Awards

Dr. Aresi - ERAB Travel Award 2010/12, ERAB Publications Award 2019.

Changing lifestyle may prevent or revert pulmonary arterial hypertension (2014) (EA 14 23)

Negrão R, Faculty of Medicine, University of Porto, Porto, Portugal

This study, using animal models, investigated whether changing lifestyle by regular consumption of beer fortified with the polyphenol xanthohumol, or regular physical exercise, or both simultaneously, could improve the prognosis of pulmonary arterial hypertension (PAH).

The results showed that consumption of alcohol (5.2%abv), had a negative effect on PAH, (causing right ventricular hypertrophy, pulmonary vascular remodelling and resistance). Consumption of the polyphenol-fortified beer, also at 5.2%abv, was found to induce beneficial effects on pulmonary remodelling and cardiovascular function. Improvements were also observed in right ventricular function and pulmonary vasculature. Regular physical exercise also had a beneficial effect on PAH but there was no cumulative beneficial effect on PAH when exercise and polyphenol-fortified beer were combined.

In summary, this animal study demonstrated the positive impact of regular physical exercise and polyphenol-rich beverages on the natural course of PAH. However, translation of these findings to humans warrants careful interpretation.

Publications

Silva AF, Faria-Costa G, Sousa-Nunes F, Santos MF, Ferreira-Pinto MJ, Duarte D, Rodrigues I, Guimarães JT, Leite-Moreira A, Moreira-Gonçalves D, Henriques-Coelho T and **Negrão R** (2019) Anti-Remodelling Effects of Xanthohumol-Fortified Beer in Pulmonary Arterial Hypertension Mediated by ERK and AKT Inhibition. *Nutrients*, 11(3):583 1-16

Rachão A, Silva AF, Nogueira-Ferreira R, Trindade F, Vitorino R, Leite-Moreira A, Moreira-Gonçalves D, Henriques-Coelho T and **Negrão R** (2017) Biological processes of polyphenols in the cardiovascular system: A bioinformatics approach: PS062. *Porto Biomedical Journal*, *2*(*5*):230

Intervention to measure impact of using unit-marked glasses for alcohol consumption in adults (2014) (EA 14 25)

de Visser RO, School of Psychology, University of Sussex, Falmer, UK

The aim of this intervention study was to test the hypothesis that using glasses marked with standard UK alcohol "units" would improve adults' knowledge of unit-based alcohol intake guidelines, their motivation to employ these guidelines, and their subsequent alcohol intake.

The "intervention" group of adult drinkers was given unit-marked plastic glasses and asked to use them for one month. A second "control" group did not receive the glasses or any instructions related to their alcohol use.

The intervention was effective at producing changes in people's understanding of, and use of unit-based guidelines to monitor their drinking. The unit-marked glasses could have an impact at the individual level (on knowledge and attitudes) and at a broader level (by prompting discussion of alcohol use). The intervention did not result in significant changes in alcohol consumption.

Publications

de Visser RO, Brown C, Cooke R, Cooper G and Memon A (2016) Using Alcohol Unit-marked Glasses Enhances Capacity To Monitor Intake: Evidence From a Mixed-method Intervention Trial. *Alcohol and Alcoholism*, 52(2):206-212

Lifestyle, social media and alcohol consumption (2014) (EA 14 33)

Szmigin I, Birmingham Business School, University of Birmingham, UK

The aim of this study was to gain insight into the relationship between alcohol consumption, social media, and lifestyle. The researchers examined this relationship in three categories: brand marketing, marketing venues, and individual young people. This was done by means of investigation of recent news reports and social media, discussions on Facebook, analysis of Twitter feeds and YouTube videos, and focus groups.

First, brand marketing mainly aims to encourage more frequent drinking. Brands try to find ways to relate any and every occasion at any time of the day to drinking. As social media is accessible 24/7, individuals can be exposed to social media advertisements 24/7, and thus be encouraged to drink all day, every day. Furthermore, brands often present alcohol as a reward and the marketing of cheap offers on social media may encourage young individuals to drink alcohol.

Second, marketing venues are highly sexualized. For example, social media advertisements regularly show scantily clad women drinking heavily. This sexualized presentation of women may lead to women being sexual harassed in bars, making women feel threatened. It is thought that it triggers aggressive sexual behavior in men to women.

The third category is individual young people. Social media often presents risky behavior around alcohol in a positive 'fun' and light-hearted manner. This media is mainly targeted at a young audience and may normalize drinking among young people. Especially taking into account that social media has a big impact on the lifestyle of young people and they feel pressure to use social media. In addition, a small group of young adults uses social media to show their alcohol misuse behavior, which may also contribute to the normalization of drinking among young individuals.

Publications

Rogan F, Piacentini M and **Szmigin** I (2016) Marketing "Raunch Culture": Sexualisation and Constructions of Femininity Within the Night-Time Economy. *ACR North American Advances*, 44:603-604

Alcohol and bleeding in the general population (2014) (EA 14 37)

Tolstrup SJ, National Institute of Public Health, University of South Denmark, Copenhagen, Denmark

Heavy drinking is linked to harmful events such as diseases of the liver and pancreas, certain cancers and heart disease. But whether alcohol affects bleeding in the general population had not been addressed. This research attempted to find an association between alcohol intake and bleeding events.

Data from two large population-based cohorts were used. Alcohol consumption was measured by self-report but also by genetic variation in genes involved in alcohol metabolism. Endpoints for bleeding included upper respiratory, gastrointestinal and urinary tract bleeding and post-operative bleeding. Also, stroke (ischemic and haemorrhagic) was included.

Heavy drinking was associated with cerebral and gastrointestinal bleeding and also with any bleeding event (bleeding events combined) compared to light alcohol consumption. In light-to-moderate drinkers there was no association between alcohol intake and all tested bleeding endpoints. More interestingly, the relative risk of both types of strokes was lower in light-to-moderate drinkers compared to non-drinkers. However, there was a tendency of an increased stroke risk in heavy drinkers. The validity of information on alcohol intake and bleeding events was tested and was found to be high based on follow-up information on liver cirrhosis and blood pressure.

In conclusion, heavy alcohol intake is associated with an increase of non-traumatic bleeding in the general population whereas light and moderate drinking is unassociated with risk of non-traumatic bleeding, which is a novel finding.

Publications

Askgaard G, Christensen AI, Nordestgaard BG, Grønbæk M and **Tolstrup JS** (2020) Alcohol and risk of non-traumatic bleeding events in the general population: A prospective cohort study. *Alcohol*, 87:73-78

Christensen AI, Nordestgaard BG and **Tolstrup JS** (2018) Alcohol Intake and Risk of Ischemic and Haemorrhagic Stroke: Results from a Mendelian Randomisation Study. *Journal of Stroke*, 20(2):218-27

The role of genetic markers of alcohol dependence, bitter taste perception, and alcohol tolerance in determining drinking patterns and the risk of breast and colorectal cancer (2015) (EA 14 39)

Simons C, Department of Epidemiology, University of Maastricht, The Netherlands

Within the Netherlands Cohort Study, two studies were conducted to investigate the association between alcohol consumption and the risk of colorectal cancer and postmenopausal breast cancer. Genetic markers, related to ethanol metabolism, were considered as effect modifiers of the associations between alcohol intake and cancer risk. The results showed that alcohol is a risk factor for colorectal cancer in men across subsites and alcohol intake levels. For women, only colon cancer risk was increased at heavy intake levels. Alcohol was also found to be a risk factor for postmenopausal breast cancer in women. Genetic variants, related to ethanol metabolism, appear to have an effect on the association between alcohol and colon cancer risk in women, but not in men nor on the association between alcohol and postmenopausal breast cancer risk in women.

Two more studies were conducted to investigate nine genetic markers of alcohol consumption or dependence, as identified as hits by previous genome-wide association studies (GWAS), in relation to alcohol consumption and the risk of colorectal cancer and breast cancer (*manuscripts in preparation*). Using GWAS markers as instrumental variables for alcohol intake to study associations with cancer risk may strengthen the evidence for a causal association. Since single genetic variants typically explain little of the variability in the exposure, we combined markers into a genetic risk score. The genetic risk score was not associated with colorectal or breast cancer risk in the Netherlands Cohort Study, nor were any of the individual genetic markers. The replicability of these particular GWAS hits was therefore low in this sample.

The analyses for genetic markers of bitter taste perception in relation to colorectal cancer and breast cancer risk are expected to be finished in 2022.

Publications

Offermans NSM, Ketcham SM, van den Brandt PA, Weijenberg MP and **Simons CCJM** (2018) Alcohol intake, *ADH1B* and *ADH1C* genotypes, and the risk of colorectal cancer by sex and subsite in the Netherlands Cohort Study. *Carcinogenesis*, 39(3):375-388

Hahn M, **Simons CCJM**, Weijenberg MP and van den Brandt PA (2018) Alcohol drinking, *ADH1B* and *ADH1C* genotypes, and the risk of postmenopausal breast cancer by hormone receptor status: The Netherlands Cohort Study on Diet and Cancer. *Carcinogenesis, 39(11)*1342–1351

More is caught than taught: a ground-breaking study on the role of implicit parenting processes on adolescents' alcohol use (2014) (EA 14 41)

Koning I, Interdisciplinary Social Science, Youth Studies, Utrecht University, The Netherlands

This research investigated the relative effect of explicit and implicit parenting cognitions on adolescents' alcohol use. Explicit parenting cognitions refer to controlled, effortful, and intentional processes, while implicit cognitions are more automatic, more likely to occur outside of conscious awareness, and are less intentional. The results suggest that both types of parenting cognitions have a different effect on adolescents' drinking behaviour over time. Stricter explicit parenting cognitions are more likely to predict a lower likelihood of ever having consumed alcohol six months later, while stricter implicit parenting cognitions predicted lower levels of weekly drinking. Moreover, these protective effects were particularly relevant for older adolescents. This means that implicit parenting cognitions are an important factor in the level of alcohol use among adolescents, even in predicting changes in behaviour over time. Strict parenting is effective in delaying the onset and reducing the amount of alcohol use even among older adolescents. It is likely that the influence of parents is subject to change as a function of adolescents' age, with the prevailing role of automatic parenting over explicit parenting.

Publications

Koning IM, Spruyt A, Doornwaard SM, Turrisi R, Heider N and De Houwer J (2017) A different view on parenting: automatic and explicit parenting cognitions in adolescents' drinking behavior. *Journal of Substance Use*, 22(1):96-101

Development and testing of a new alcohol attentional bias modification training paradigm: What are its neurocognitive mechanisms of action and how do they relate to real-life drinking behaviours? (2014) (EA 14 42)

Nikolaou K, Department of Psychology, Universiteit van Amsterdam, The Netherlands

This aim of this research was to validate a novel internet-based method of alcohol attentional bias re-training. With this method, participants are consistently trained to ignore stimuli associated with alcohol. This training would reduce attentional biases to alcohol-associated stimuli, and reduce alcohol consumption and craving. Results from a student population of social drinkers suggested that the training had a small effect on biases to alcohol related cues. Minor effects were found on alcohol drinking and alcohol craving. Additional analyses suggest that this type of training may be more beneficial to individuals with higher biases to alcohol cues, more severe alcohol use and higher levels of impulsivity before the start of the training. More research is needed to assess the effects of the training in bigger samples of patients with alcohol dependence.

Publications

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Effects of alcohol consumption on gut microbiota composition in adults (ALMICROBHOL) (2014) (EA 14 44)

Marcos A, Institute of Food Science, Technology and Nutrition (ICTAN), Spanish National Research Council, Madrid, Spain

The Almicrobhol study has been carried out by the Immunonutrition research group headed by Dr. Ascensión Marcos and Dr. Esther Nova. This study investigated whether the pattern of alcohol consumption (alcohol amount, frequency of consumption, binge- or regular-drinking) as well as the different types of alcoholic fermented and distilled beverages influence the gut microbiota composition of healthy adult individuals. Participants were recruited in both Spain and Slovenia. 261 valid cases were included from Spain and 134 from Slovenia.

Gut microbiota composition from frozen faecal samples was analysed, centrally, through 16S rRNA sequencing and taxa identification by comparative rRNA taxonomy. The contribution of beer to alcohol consumption (8.4 g/d) was significantly higher than that of wine (2.8 g/d) in this population. The mean daily grams of alcohol consumption were positively associated with abundance of the genera *Borrelia*, *Erysipelothrix* and *Paraprevotella* (all, r=0,178; P=0,010). Daily grams of alcohol from beer were directly associated with *Chryseobacterium* and *Erysipelothrix* but no relevant association was found between amount of wine intake and the microbiota genera. Excessive weekend consumption was associated with a decrease in beta diversity. There were no differences among pattern consumption groups regarding the main phyla and genus analysed.

Conclusions: The amount of alcohol consumption may influence the abundance of minor genera in the microbiota and beer intake was related to some of the changes observed.

Publications

González-Zancada N, Redondo-Useros N, Díaz LE, Gómez-Martínez S, **Marcos A** and Nova E (2020). Association of Moderate Beer Consumption with the Gut Microbiota and SCFA of Healthy Adults. *Molecules*, 25(20):4772. doi: 10.3390/molecules25204772

Bezek K, Petelin A, Pražnikar J, Nova E, Redondo N, **Marcos A** and Pražnikar ZJ (2020) Obesity Measures and Dietary Parameters as Predictors of Gut Microbiota Phyla in Healthy Individuals. *Nutrients*, 12(9):2695 doi: 10.3390/nu12092695

Evaluation of moderate daily intake of beer in reducing menopausal symptoms. Estrogenic effect of hop prenylflavanoids (2015) (EA 15 14)

Tresserra Rimbau A, Department of Nutrition and Food Science, School of Pharmacy, University of Barcelona, Barcelona, Spain

Hop prenylflavonoids are compounds with estrogen-like properties. The hypothesis was that these phytoestrogens could therefore alleviate menopausal symptoms. This hypothesis was addressed in a parallel controlled clinical trial. The effect of the intervention on the female sex hormone profile and cardiovascular risk factors was also monitored.

A total of 37 post-menopausal women were assigned and followed to either drink no beer, one alcoholic beer a day or two non-alcoholic beers a day for 6 months. Samples of blood, urine, physical activity and dietary assessments were collected. In addition, questionnaires were taken to evaluate the Menopause Rate Scale (MRS). It appeared that total menopausal symptoms decreased significantly with the regular beer and non-alcoholic beer interventions in comparison to the control group. However, the psychological symptoms were only significantly decreased in the alcoholic beer group. The three most frequently experienced symptoms of the eleven composing the MRS were joint and muscular discomfort (70.3%), physical and mental exhaustion (70.3%) and sleep problems (64.9%). More research is needed before moderate beer consumption can be recommended to decrease the uncomfortable symptoms of menopause, reduce medication and improve the quality of life.

Publications

Sandoval-Ramírez BA, Lamuela-Raventós RM, Estruch R, Sasot G, Doménech M and **Tresserra-Rimbau A** (2017) Beer Polyphenols and Menopause: Effects and Mechanisms-A Review of Current Knowledge. *Oxidative Medicine and Cellular Longevity*, 4749131. https://doi.org/10.1155/2017/4749131

Risks and benefits of moderate beer intake (with and without alcohol) on osteoporosis in postmenopausal women (2015) (EA 15 15)

Lamuela-Raventós RM, Department of Nutrition, Food Science and Gastronomy, School of Pharmacy and Food Sciences, University of Barcelona, Barcelona, Spain

The hypothesis of this study was that moderate beer consumption may help to prevent osteoporosis in postmenopausal women due to its phenolic, silicon and ethanol content. It should provide beneficial effects on bone tissue, stimulating human osteoblasts formation, reducing bone fragility, and increasing bone mineral density.

To test this hypothesis, the researchers included thirty-seven recent postmenopausal women in a parallel, controlled clinical intervention trial. The participants were devided into three groups: regular beer (330 mL/day), non-alcoholic beer (660 mL/day), or the control (no beer). The length of the intervention was two years.

Results showed that markers of bone formation and bone resorption increased in both intervention groups compared to the control group, although these changes were only significant in N-terminal propeptide of type I collagen levels for both intervention groups and for bone alkaline phosphatase for the non-alcoholic beer group (both markers of bone formation). Total bone mineral density and trabecular bone score decreased over time in intervention groups.

In summary, the intake of one regular beer or two non-alcoholic beers a day for two years seems to increase molecular mediators of bone formation. Despite this, bone mineral density and trabecular bone score at follow-up showed no effect on osteoporosis after moderate daily regular beer consumption in menopausal women. However, the sample of this study is too small to draw conclusions. Future studies with a higher sample size are needed to understand the role of moderate beer consumption and its components (ethanol, silicon, polyphenols) on osteoporosis.

Publications

Trius-Soler M, Marhuenda-Muñoz M, Laveriano-Santos EP, Martínez-Huélamo M, Sasot G, Storniolo CE, Estruch R, **Lamuela-Raventós RM** and Tresserra-Rimbau A, (2021) Moderate Consumption of Beer (with and without Ethanol) and Menopausal Symptoms: Results from a Parallel Clinical Trial in Postmenopausal Women. *Nutrients*, 13(7):2278. doi: 10.3390/nu13072278

Trius-Soler M, Vilas-Franquesa A, Tresserra-Rimbau A, Saso, G, Storniolo CE, Estruch R and **Lamuela-Raventós RM** (2020) Effects of the Non-Alcoholic Fraction of Beer on Abdominal Fat, Osteoporosis, and Body Hydration in Women. Molecules, 25(17),3910. doi.org/10.3390/molecules25173910

Health effects of the ethanol and polyphenol content in beer: Evaluation of the effects of moderate beer consumption on cardiovascular system. A metabolomic approach. (2015) (EA 15 17)

Medina-Remon A, Department of internal Medicine, Hospital Clinic, University of Barcelona, Spain

This research consisted of a randomized controlled trial including 33 males between 55 and 75 years old. Participants underwent three interventions including beer, non-alcoholic beer, and gin, in a random order for four weeks each intervention. The researchers performed a metabolomic analysis on the urine and found two potential new biomarkers for beer and non-alcoholic beer consumption (Humulinone and 2,3-dihydroxy-3-methylvaleric acid). Additionally, the results suggested that regular and moderate beer and non-alcoholic beer consumption may increase fatty acid oxidation.

Publications

Quifer-Rada P, Chiva-Blanch G, Jáuregui O, Estruch R and Lamuela-Raventós RM (2017) A discovery-driven approach to elucidate urinary metabolome changes after a regular and moderate consumption of beer and non-alcoholic beer in subjects at high cardiovascular risk. *Molecular Nutrition and Food Research*, 61(10):1600980

Quifer-Rada P, Martínez-Huélamo M and Lamuela-Raventós RM (2017) Is enzymatic hydrolysis a reliable analytical strategy to quantify glucuronidated and sulfated polyphenol metabolites in human fluids? *Food and Function*, 8(7):2419-2424

Activation of the human innate immune system and anticancer properties mediated by hop-derived prenylflavonoids naturally enriched in beer (2015) (EA 15 28)

Venturelli S, Department of Internal Medicine, University Hospital of Tuebingen, Tuebingen, Germany. Now at the Department of Nutritional Biochemistry, University of Hohenheim, Stuttgart, Germany.

The hop-derived prenylflavonoids 6-prenylnaringenin and 8-prenynaringenin (PN) seem to inhibit the proliferation of cancer cells and stimulate the innate immune system. However, the exact molecular mechanisms remain unexplored. In this study different cell types of the immune system (natural killer cells; NK-cells), tumour cells (melanoma and liver) and healthy liver cells were exposed to both PN. To the researchers' surprise, the PN did not modulate common markers of NK-cells, which suggests that the enhanced tumour cell killing of NK-cells is driven by more complex molecular mechanisms. Further research explored that PN downregulated the oncogenic S6 protein in tumour cells. This affects tumour cell survival and proliferation and makes tumour cells more sensitive for killing by NK-cells. In addition, PN treated NK-cells had an upregulation of perforin and granzyme A/B which improve their killing efficacy. The PN were very well tolerated by healthy cells, which make these natural hop constituents even more valuable. In conclusion, PN increase the visibility of cancer cells to the immune system and at the same time stimulate the NK-cells ability to destroy cancer cells. Because of the excellent tolerability of these prenylflavonoids, they could be promising for immunologic cancer therapy.

Publications

Venturelli S, Niessner H, Sinnberg T, Berger A, Burkard M, Urmann C, Donaubauer K, Böcker A, Leischner C, Riepl H, **Frank J**, Lauer UM, Garbe C and Busch C (2018) 6- and 8-Prenylnaringenin, Novel Natural Histone Deacetylase Inhibitors Found in Hops, Exert Antitumor Activity on Melanoma Cells. *Cellular Physiology and Biochemistry*, 52(2):543-556. DOI: 10.1159/000495275

Sus N, Schlenz J, Calvo-Castro, LA, Burkard M, **Venturelli S**, Busch C and **Frank J** (2018) Validation of a rapid and sensitive reversed- phase liquid chromatographic method for the quantification of prenylated chalcones and flavanones in plasma and urine. *NFS Journal*, 10:1-9. DOI: j.nfs.2017.11.001

Burkard M, Kohl S, Krätzig T, Tanimoto N, Brennenstuhl C, Bausch AE, Junger K, Reuter P, Sothilingam V, Beck SC, Huber G, Ding XQ, Mayer AK, Baumann B, Weisschuh N, Zobor D, Hahn GA, Kellner U, **Venturelli S**, Becirovic E, Charbel Issa P, Koenekoop RK, Rudolph G, Heckenlively J, Sieving P, Weleber RG, Hamel C, Zong X, Biel M, Lukowski R, Seeliger MW, Michalakis S, Wissinger B and Ruth P (2018) Accessory heterozygous mutations in cone photoreceptor CNGA3 exacerbate CNG channel-associated retinopathy. *The Journal of Clinical Investigation*, 128(12):5663-5675 DOI: 10.1172/JCI96098

Calvo-Castro LA, Burkard M, Sus N, Scheubeck G., Leischner C, Lauer UM, Bosy-Westphal A, Hund V., Busch C, **Venturelli S** and **Frank J** (2018) The oral bioavailability of 8-prenylnaringenin from hops (Humulus lupulus L.) in healthy women and men is significantly higher than that of its positional isomer 6-prenylnaringenin in a randomized crossover trial. *Molecular Nutrition and Food Research*, 62(7):1700838. DOI: mnfr.201700838

Burkard M, Leischner C, Lauer UM, Busch C, **Venturelli S** and **Frank J** (2017) Dietary flavonoids and modulation of natural killer cells: Implications in malignant and viral diseases. Review article; *Journal of Nutritional Biochemistry*, 46:1-12. DOI: 10.1016/j.jnutbio.2017.01.006

Aschermann I, Noor S, **Venturelli S**, Sinnberg T, Mnich CD and Busch C (2017) Extracorporal shock waves activate migration, proliferation and inflammatory pathways in fibroblasts and keratinocytes, and improve wound healing in an open-label, single-arm study in patients with therapy-refractory chronic leg ulcers. *Cellular Physiology and Biochemistry*, 41(3):890-906.

Ellerhoff T, Berchtold S, Venturelli S, Burkard M, Smirnow I, Wulff T and Lauer UM (2016) Novel epi-virotherapeutic treatment of pancreatic cancer combining the oral histone deacetylase inhibitor resminostat with oncolytic measles vaccine virus. International Journal of Oncology, 49(5):1931-1944 DOI: 10.3892/ijo.2016.3675

Theses and Awards

Professors Venturelli and Frank and Dr. Busch - joint ERAB Publications Award 2020

A study on young drinking behaviour - evaluation of the relationship between taste reactivity and special beer consumption (2015) (EA 15 45)

Salanță L-C, University of Agricultural Sciences and Veterinary Medicine, Cluj-Napoca, Romania

This aim of this research was to evaluate the role of sensory characteristics in the perception, preference and consumption of low- and non-alcoholic beer among university students from Romania. The results showed that students' perception of low- and non-alcoholic beer quality was based on a complex mix of expectations, which are generally associated with some sensory attributes such as colour, foam, flavour and aroma, mouthfeel and aftertaste.

95% of university students have consumed low-alcoholic beer, and 8.8% of them declared that they did not like it. Non-alcoholic beer was consumed by 84% of the students, and 38% indicated that they did not like it because of poor flavour profile. Students who liked the low- and non-alcoholic beers were attracted by flavour and aroma (79.4%), low concentration of alcohol (11%) and colour (0.9%) of the beer. Students who indicated that they did not like the beer, claimed a poor aroma, CO_2, taste and foam.

Obtaining low alcohol content via interrupted fermentation is accompanied by low content of aroma and flavour compounds, and the products are often characterized by worty off-flavours. This research indicates that flavour appears to play an important positive role for students. Additionally, anticipated emotions and feelings associated with beer consumption is also a motivation for their choice.

Publications

Salanţă LC, Tofană M, Pop C, Pop A, Coldea T and Mihai M (2018) Risk Factors Associated with Alcohol Consumption Among Romanian University Students-Preliminary Research. *Bulletin UASVM Food Science and Technology*, 75(1):86-89

Salanţă LC, Tofană M, Pop C, Pop A, Coldea T and Mudura E (2017) Beverage Alcohol Choice Among University Students: Perception, Consumption and Preferences. *Bulletin UASVM Food Science and Technology*, 74(1):23-30

Salanţă LC, Tofană M, Mudura E, Pop C, Pop A and Coldea T (2016) The alcoholic beverage consumption preference of university students: a preliminary Romanian case study. *Bulletin UASVM Food Science and Technology*, 73(1):31-39

Peer influence and alcohol cognitions: Understanding the interaction between implicit processes and peer context (2015) (EA 15 49)

Larsen H, Department of Psychology, University of Amsterdam, Amsterdam, The Netherlands.

The aim of this project was to investigate the interplay between peer context and implicit, automatic alcohol identity cognitions, in relation to alcohol consumption in emerging adults. It also investigated whether conversational valence would mediate the association between online peer chats and drinking identity, and whether automatic identity cognitions can be altered.

This research found that the implicit drinking identity of heavy drinkers is influenced by their social context. Online chat sessions with peers, with and without alcohol-related content, activates these automatic alcohol cognitions in heavy (but not light) drinkers. This effect was found, however, in both chat conditions, but not in the condition where there was no peer interaction, indicating that merely the interaction with peers might be sufficient to elicit automatically activated implicit drinking cognitions. This suggests that online chat and peer influence can impact implicit drinking identities, compared to when a peer is not involved in the interaction. Examination of the mediating effects of conversational valence during chat sessions demonstrated that conversation valence can explain the relationship between peer context and implicit drinking identity. This suggests that when participants are talked to by their peers about alcohol, they are more likely to respond positively, which in turn increases their implicit drinking identity. This effect is significantly stronger than when participants are talked to by their peers about regular topics, which suggests that how peers interact online needs to be given strong consideration.

In addition, this project revealed the challenges that arise with the altering of automatic drinking identity cognitions. The reason for this may be that identity is dependent on the context and therefore it is difficult to measure change. The results did confirm previous research indicating a positive relationship between the implicit drinking identity and urge to drink and after controlling for explicit drinking identity. Interestingly, the implicit drinking identity predicted amount of alcohol consumption in the 'drinker+me' condition only, and not in the 'abstainer+me' condition. This indicates that drinking identity may differ in the prediction of alcohol consumption dependent on the exposure to a training where they are asked to identify as a drinker versus as a non-drinker.

In summary, leaving aside the possible impact social contexts, (such as online peer chat) have on implicit alcohol cognitions such as drinking identity, interventions may not influence heavy drinkers' alcohol consumption as effectively as possible. It is especially important to focus on the norms in terms of how young adults talk about alcohol. It can be beneficial to talk less positively about alcohol and focus on helping people to identify as a non-drinker instead of as a drinker.

Publications

Larsen H, Van Bockstaele B, Martens N, Wills E and Wiers RW (Submitted for publication) Using the Relational Responding Task to Alter Drinking Identity Associations: An Experimental Study.

Larsen H, Hagen A, Van Bockstaele B, Hendriks H, Scholz C, van den Putte B and Wiers RW (Submitted for publication) The Effect of Online Peer Influence on Implicit Drinker Identity: An Experimental Study.

Dissociating Impulsivity and Reward Processing Endophenotypes of Alcohol Misuse Patterns (2015) (EA 15 50)

Whelan R, Institute for Neurosciences, Trinity College Dublin, Dublin Ireland

Impulsivity (the ability to control our actions) and reward processing (the way we learn from feedback subsequent to our actions) are central to understanding the causes of alcohol misuse. Both impulsivity and reward processing can be further subdivided into separate components. Impulsivity can be separated into impulsive action and impulsive choice. This research found that impulsive choice could distinguish those who got drunk frequently (but wasn't associated with how often people drank alcohol). A further study showed that brain measures of impulsivity could also distinguish those who consumed alcohol to excess.

With respect to reward processing, the investigators looked at the differences between the reward that people expect to receive and what they actually receive – the 'reward prediction error'. Brain differences associated with reward prediction errors could be detected, and these brain differences could distinguish those with problematic alcohol consumption. Problematic alcohol consumption was associated with exaggerated reward prediction errors.

Summarized, this research has shown that high alcohol consumption is related to specific psychological characteristics. Heavy drinkers were characterized by differences in both impulsivity and in reward processing. Notably, these differences were present specifically for heavy drinking, and were not found in alcohol consumers in general.

Publications

Cao Z, Bennett M, O'Halloran L, Pragulbickaite G, Flanagan L, McHugh L and **Whelan R** (2021) Aberrant reward prediction errors in young adult at risk alcohol users. *Addiction Biology*, doi: 10.1111/adb.12873

O'Halloran L, Rueda-Delgado LM, Jollans L, Cao, Z, Boyle R, Vaughan C, Coey P and **Whelan R** (2019) Inhibitory-control event-related potentials correlate with individual differences in alcohol use. *Addiction Biology*, 1-11. DOI: 10.1111/adb.12729

O'Halloran L, Pennie B, Jollans L, Kiiski H., Vahey N., Rai L, Bradley L, Lalor R and **Whelan R** (2018) A Combination of Impulsivity Subdomains Predict Alcohol Intoxication Frequency. *Alcoholism: Clinical and Experimental Research*, 42(8):1530-1540

Padilla MM, O'Halloran L, Bennett M, Cao Z and **Whelan R** (2017) Impulsivity and Reward Processing Endophenotypes in Youth Alcohol Misuse. *Current Addiction Reports*, 4(4):350–363. DOI 10.1007/s40429-017-0167-6

O'Halloran L, Nymberg C, Jollans L, Garavan H and **Whelan R** (2017) The potential of neuroimaging for identifying predictors of adolescent alcohol use initiation and misuse. *Addiction*, 112(4),719-726. https://doi.org/10.1111/add.13629

Theses and Awards

Dr. Whelan - ERAB Publications Award 2020

Alcohol consumption in daily life: A mobile ecological momentary assessment study in a general population sample (2016) (EA 16 34)

Jacobs N, Faculty of Psychology and Educational Sciences, Open University, DL Heerlen, The Netherlands

Despite an abundance of alcohol-related studies, few studies have focused on alcohol-associated lifestyle factors in the context of daily life. This research assessed the alcohol consumption and contextual factors in a Dutch general population sample of 305 adults, using a mobile ecological momentary assessment approach.

Various hypotheses were tested on alcohol intake related to social context, affect, and stress reactivity. Results show that both positive and negative feelings may trigger the decision to drink alcohol. Individuals may decide to consume alcohol when they experience emotional ups and downs. Additionally, when negative feelings are salient, individuals may consume greater quantities of alcohol. Negative affect may play a crucial role in the stress-alcohol relationship. In particular, when negative affect is elevated, stress may evoke alcohol consumption. The overall conclusion is that emotions may evoke alcohol consumption in non-dependent, moderately drinking adults.

Publications

Duif M, Thewissen V, Wouters S, Lechner L and **Jacobs N** (2019) Stress, Negative Affect, and Alcohol Consumption in Daily Life: An Ecological Momentary Assessment Study in an Adult Sample. *The American Journal of Drug and Alcohol Abuse*, 46(1):1-10. DOI: 10.1080/00952990.2019.1635606

Duif M, Thewissen V, Wouters S, Lechner L and **Jacobs N** (2019) Affective Instability and Alcohol Consumption: Ecological Momentary Assessment in an Adult Sample. *Journal of Studies on Alcohol and Drugs*, 80(4):441–447.

Duif M, Thewissen V, Wouters S, Lechner L and **Jacobs N** (2019) Associations between affect and alcohol consumption in adults: an ecological momentary assessment study. *The American Journal of Drug and Alcohol Abuse*, DOI: 10.1080/00952990.2019.1635606

To consider the health effects arising from the components of beer (brewed at large and small scale) in particular, to investigate the effect of folate and vitamin B6 content of beer on serum homocysteine and the cardiovascular system. (2016) (EA 16 37)

Bertuzzi T, Catholic University of the Sacred Heart, Milan, Italy

This research investigated the perceptions of consumers, the composition and the cardiovascular health effects of small-scale and large-scale brewed beers. Questionnaires were shared on paper and electronically to study the patterns of consumption, the preferences and attitudes towards small-scale and large-scale brewed beers. Next, various samples of small-scale and large-scale brewed

beers were analysed for their composition (such as vitamins and phenols, but also undesirable compounds). And finally, an intervention trial was performed to evaluate the effect of moderate beer consumption on the cardiovascular system.
The results showed that perceptions depended on the type of beer the consumer is used to drinking; small-scale brewed beer evoked more emotional and sensory experience and large-scale brewed beer was associated more with convenience. Differences in nutrient composition were found between different styles of beer, but rarely between small-scale and large-scale brewed beers of similar style. With regard to undesirable compounds, low levels of both mycotoxins and amines and heavy metals were found in all beers. Daily moderate beer consumption (about 1 alcoholic unit) increased folate levels, but not vitamin B6. Higher folate levels are inversely correlated with homocysteine levels. Homocysteine is a known risk factor for cardiovascular disease. This suggests that moderate daily beer consumption may protect the cardiovascular system.

Publications

Romanini E, Rastelli S, Donadini G, Lambri M and **Bertuzzi T** (2021) Pyridoxine and folates during small- and large-scale brewing. *Journal of the Institute of Brewing*, 127:135-139.

Donadini G, **Bertuzzi T**, Rossi F, Spigno G and Porretta S (2020) Uncovering Patterns of Italian Consumers' Interest for Gluten-Free Beers. *Journal of the American Society of Brewing Chemists*, 79:4

Rossi F, Spigno G, Luzzani G, Bozzoni ME, Donadini G, Rolla J and **Bertuzzi T** (2020) Effects of the intake of craft or industrial beer on serum homocysteine. *International Journal of Food Sciences and Nutrition*, 72(1):93-98. doi:10.1080/09637486.2020.1760219

Donadini G, **Bertuzzi T**, Kordialik-Bogacka E, Cywińska D, Rossi F, Spigno G and Poretta S (2020) Investigating patterns of millennials' interest in gluten-free beer in Poland: A question of beer price and alcohol content. *Journal of Food Science*, 85(1):182-191. doi.org/10.1111/1750-3841.14985

Bertuzzi T, Mulazzi A, Rastelli S, Donadini G, Rossi F and Spigno G (2020) Targeted healthy compounds in small and large-scale brewed beers. *Food Chemistry*, 310:125935. doi.org/10.1016/j.foodchem.2019.125935

Bertuzzi T, Rastelli S, Mulazzi A and Rossi F (2019) LC-MS/MS Determination of Mono-Glutamate Folates and Folic Acid in Beer. *Food Analytical Methods*, 12(3):722-728. https://doi.org/10.1007/s12161-018-1396-6

Bertuzzi T, Rastelli S, Mulazzi A, Donadini G and Pietri A (2018) Known and Emerging Mycotoxins in Small- and Large-Scale Brewed Beer. *Beverages*, *4*(2):46. https://doi.org/10.3390/beverages4020046

Binging on alcohol and social stress in adolescence: a translational research in Sicily (BASTA) (2016) (EA 16 42)

Cannizzaro C, Department of Sciences for Health Promotion and Mother and Child, University of Palermo, Italy

This study explored the impact of binge drinking in adolescence on the vulnerability and resilience to psychosocial stress, and on underpinning markers of neurobiological response to stress and natural stimuli, from a translational perspective.

The prevalence of binge drinking and its correlation to a specific psychological profile, as well as the consequences on neuroendocrine responses were evaluated in response to a social-evaluative threat in late adolescents of both sexes, recruited from high schools in Palermo, Italy. The assessment of the binge-behavioural phenotype was subsequently modelled in adolescent rats to explore the underlying neurobiological mechanisms.

Results showed a weak ability to cope with stress by adolescent binge drinkers (altered HPA axis), as well as a prevalence of clinical syndrome and personality disorders according to the drinking pattern. In the animal model, decreased social behaviour, increased anxiety- and depressive-like behaviour, high sensitivity to pain, and an impaired defensive behaviour persisted even after 10 days of withdrawal. Indeed, rats exposed to binge drinking had more trouble dealing with social and stress-inducing challenges in late abstinence. Experiments showed that this was related to aberrant expression of markers of stress processing, excitatory pre- and postsynaptic signalling and neuronal plasticity in the nucleus accumbens, the motivational and integrational hub of the mesocorticolimbic system.

In view of the role played by cultural and social environmental challenges during adolescence, failure to face and cope with stressful situations may represent the gateway to depression and anxiety-related disturbances later in life. Thus, rehabilitation programs should be developed to improve self-reliance and resilience abilities in the early stages of alcohol-related disorders. Furthermore, the employment of promising therapeutics for the treatment of alcohol-related consequences, need to be carefully evaluated, in the light of their broad and complex effects on neurobiology and behaviour.

Publications

Brancato A, Castelli V, Lavanco G, Tringali G, Micale V, Kuchar M, D'Amico C, Pizzolanti G, Feo S, **Cannizzaro C** (2021) Binge-like alcohol exposure in adolescence: from intoxication to withdrawal. Behavioral, neuroendocrine and molecular evidence of abnormal neuroplasticity…and return. Biomedicines 2021 Sep 4;9(9):1161.doi: 10.3390/biomedicines9091161

Less spirit, more wine and beer: predictors, mediators and health consequences of drinking patterns in contemporary Sweden (2016) (EA 16 45)

Möller J, Department of Public Health Science, Karolinska Institute, Stockholm, Sweden

The study examined the drinking patterns of contemporary Swedish drinkers at three time points and identified specific drinking trajectories and predictors thereof. Most individuals were stable in their drinking pattern over time, in particular wine drinkers. Stable low- or-moderate alcohol consumption appeared to be associated with the best baseline health and the most favourable lifestyle. Other trajectories were mainly associated with poorer self-rated health, lower social support, and unfavourable socioeconomic circumstances (in particular, stable and unstable non-drinkers, and former drinkers) and unhealthy behaviour at baseline (in particular, stable and unstable heavy drinkers). The predictors for hazardous drinking patterns were in line with that expected from earlier studies.

The study also found a U-shaped association between alcohol trajectories and self-rated health but not for psychological distress. While stable moderate drinking was associated with the lowest odds of poor self-rated health, former drinking was associated with the highest odds of poor self-rated health and psychological distress. The results remained after taking other health, lifestyle and sociodemographic factors into account. The study confirms the importance of a life-course approach to examining the effect of alcohol consumption on health.

Publications

Sidorchuk A, Gemes K, Engström K, **Möller J** (submitted) Predictors of beverage-specific alcohol consumption trajectories: a Swedish population-based cohort study.

Gemes K, **Möller J**, Engström K and Sidorchuk A (2019) Alcohol consumption trajectories and self-rated health: findings from the Stockholm Public Health Cohort. *BMJ Open,* 9:e028878. doi:10.1136/bmjopen-2018-028878

Role of liver progenitor cells in the progression of alcoholic liver disease (2016) (EA 16 53)

Sancho-Bru P, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain

It is hypothesized that specific gene signatures from human liver progenitor cells (LPCs) and functional molecular networks are associated with progression of alcoholic liver disease (ALD), clinical prognosis variables, degree of regeneration potential and overall survival. To study this, the researchers identified gene expression networks associated with clinical outcomes in patients with ALD, and investigated the relationship between LPCs and the local and systemic inflammatory response in ALD. Results showed that ductular reaction (DR) cells as well as LPCs have a pro-inflammatory profile with expression of CXC and CCL chemokines and are associated with neutrophil infiltration. In addition, liver organoids mimic liver DR, thus being a good *in vitro* model to study DR cells, and promote neutrophil migration and inflammation. This research revealed the role of liver progenitor cells in alcoholic liver disease and shed light on their contribution to the progression of the disease. Moreover, these findings lay the foundation for new therapeutic strategies aiming at reducing pro-inflammatory phenotype of LPC to reduce liver inflammation and promote liver regeneration.

Publications

Coll M, Ariño S, Martínez-Sánchez C, Garcia-Pras E, Gallego J, Moles A, Aguilar-Bravo B, Blaya D, Vallverdú J, Rubio-Tomás T, Lozano JJ, Pose E, Graupera I, Fernández-Vidal A, Pol A, Bataller R, Geng JG, Ginès P, Fernandez M and **Sancho-Bru P** (2022) Ductular reaction promotes intrahepatic angiogenesis through Slit2-Roundabout 1 signaling. *Hepatology*, 75(2):353-368. doi: 10.1002/hep.32140. Epub 2021 Dec 15. PMID: 34490644; PMCID: PMC8766889

Aguilar-Bravo B and **Sancho-Bru P** (2019) Laser capture microdissection: techniques and applications in liver diseases. *Hepatology International,* 13*(2):*138–147

Aguilar-Bravo B, Rodrigo-Torres D, Arino S, Coll M, Pose E, Blaya D, Graupera I, Perea L, Vallverdu J, Rubio-Tomas T, Dubuquoy L, Armengol C, Lo Nigo A, Atärkel P, Methurin P, Batallier R, Caballeria J, Lozano JJ, Ginès P and **Sancho-Bru P** (2018) Ductular reaction cells display an inflammatory profile and recruit neutrophils in alcoholic hepatitis. *Hepatology*, 69(5):2180-2195

Blaya D, Aguilar-Bravo B, Hao F, Casacuberta-Serra S, Coll M, Perea L, Vallverdu J, Graupera I, Pose E, Llovet L, Barquinero J, Cubero FJ, Caballeria J Ginès P and

Sancho-Bru P (2018) Expression of microRNA-155 in inflammatory cells modulates liver injury. *Hepatology*, *68(2)*:691–706

Moderate beer intake effects on the inflammasome pathway and TLR-mediated immunomodulation in humans (2016) (EA 16 59)

Badimon L, Cardiovascular Research Center (CSIC-ICCC), Hospital de la Santa Cruz y San Pablo, Barcelona, Spain

Consistent epidemiological evidence indicates that low-to-moderate alcohol consumption is inversely associated with cardiovascular event presentation, while high levels of alcohol intake are associated with increased cardiovascular risk. Little is known on the effects of moderate beer intake in the metabolic syndrome. The aim of this study was to investigate the effects of moderate and regular daily intake of beer with meals in overweight or obese individuals without other cardiovascular risk factors.

The researchers performed an open, prospective two-arms longitudinal crossover study to investigate the effects associated with regular consumption of alcohol-free-beer or traditional-beer (30 g alcohol/day in men and 15 g alcohol/day in women) on anthropometrical and biochemical parameters, liver and kidney function biomarkers, and vascular endothelial function, as well on the modulation of the functional behavior of cultured human macrophages when exposed to external pro-inflammatory stimulus.

After a four-week intervention with traditional and/or alcohol-free beer, BMI did not show any significant change and values for liver, and kidney functions were within the normal levels. Moderate traditional beer intake did not affect lipid levels. However, it significantly increased the antioxidant capacity of high density lipoprotein (HDL). In addition, apoB-depleted serum showed a higher potential to promote cholesterol efflux from macrophages. Beer consumption did not induce vascular endothelial dysfunction or stiffness. Serum of moderate beer consumers attenuated the inflammasome signaling.

In conclusion, the results provide evidence that moderate intake of beer does not exert detrimental vascular effects, nor does it increase body weight in obese healthy individuals. In contrast, moderate intake of beer increases the anti-oxidative properties of HDL and facilitates cholesterol efflux, which may prevent lipid deposition in the vessel wall.

Publications

Muñoz-Garcia N, Escate R, **Badimon L**, and Padro T (2021) Moderate Beer Intake Downregulates Inflammasome Pathway Gene Expression in Human Macrophages. *Biology*, *10*(11), 1159

Padro T, Muñoz-García N, Vilahur G, Chagas P, Deyà A, Antonijoan R M, and **Badimon L** (2018) Moderate beer intake and cardiovascular health in overweight individuals. *Nutrients*, *10*(9), 1237

Pharmacological characterization of the novel positive allosteric modulator of the $GABA_B$ receptor, COR659: focus on its "anti-alcohol" effects (2017) (EA 17 14)

Maccioni P, Neuroscience Institute, Section of Cagliari, National Research Council of Italy [*Consiglio Nazionale delle Ricerche* (CNR)], Cagliari, Italy

The aim of this research project was to further characterise the "anti-alcohol" pharmacological profile of COR659, investigating its possible suppressing effect on multiple alcohol-related behaviours. COR659 is a positive allosteric modulator of the $GABA_B$ receptor that acts by potentiating the function of the neurotransmitter GABA at the $GABA_B$ receptor. To further characterize COR659, preclinical screening was performed in a validated rat model of human alcohol use disorder. Rat experiments showed that COR659 was able to reduce craving-like behaviour, heavy and binge-like drinking and "relapse" into heavy drinking. The researchers further looked into the mechanism and speculated that $GABA_B$ receptors in a specific brain "reward" region explain the alcohol reducing effects of COR659. Moreover, COR659 proved to be a potent compound with limited development of tolerance after repeated use. Doses of COR659 used in the experiments did not induce sedation or impaired motor skills. In conclusion, COR659 could be a promising therapeutic to control alcohol use disorder in humans.

Publications

Colombo G, Lobina C, **Maccioni P**, Mugnaini C and Corelli F (in preparation) Reducing effect of the positive allosteric modulator of the $GABA_B$ receptor, COR659, on alcohol drinking in rats: Development of tolerance on continuing treatment.

Lorrai I, Shankula C, Gaytan JM, Kawamura T, **Maccioni P**, Mugnaini C, Corelli F, Gessa GL, Sanna PP and Colombo G (2022) Reducing effect of the novel positive allosteric modulator of the $GABA_B$ receptor, COR659, on binge-like alcohol drinking in male mice and rats. *Psychopharmacology*, 239(1): 201-213

Ferlenghi F*, **Maccioni P***, Mugnaini C*, Brizzi A, Fara F, Mostallino R, Corelli F (2020) The $GABA_B$ receptor positive allosteric modulator COR659: In vitro metabolism, in vivo pharmacokinetics in rats, synthesis and pharmacological characterization of metabolically protected derivatives. *European Journal of Pharmaceutical Sciences*, 155,105544. *: equal contribution

In vivo evaluation of the effects of alcohol exposure on cell proliferation (2017) (EA 17 19)

Toietta G, Department of Research, Advanced Diagnostic and Technological Innovation, Regina Elena National Cancer Institute, Rome, Italy

Ethanol assimilated with alcoholic beverages is enzymatically metabolized in the body to acetaldehyde, that is then further oxidized to acetate. This process alters the cellular redox status and generates reactive oxygen species that may produce DNA damage. In addition, acetaldehyde causes the formation of DNA adducts that inhibit DNA repair systems and interfere with DNA replication. Consequently, acetaldehyde, along with alcoholic beverages, is considered as "carcinogenic to humans" by the World Health Organization International Agency for Research on Cancer.

The biological consequences and implications of acquired genetic lesions induced by ethanol metabolism have a profound influence on stem cell function. In particular, a severe loss of functional hematopoietic stem cells may result from the alteration of the molecular and mechanical cues in bone marrow microenvironment (niche) induced by acetaldehyde toxicity. This suppresses physiological haematopoiesis and ultimately reduces the organism's capacity to fight against cancer, infections and to promote tissue regeneration.

To elucidate *in vivo* the cellular mechanisms associated with alcohol intake toxicity a mouse model was used in which proliferating cells produce the firefly's light-emitting protein. In this animal, alcohol exposure transiently "turns off the light" indicating a detrimental effect on bone marrow and splenic cell proliferation. Pharmacological treatment with substances interfering with alcohol metabolism, reducing acetaldehyde production, partially restores the physiological cell

proliferation rate. Furthermore, this research confirmed the detrimental effect of alcohol exposure on proliferation of primary stromal cells isolated from healthy donors cultured *in vitro*.

These results contribute to the elucidation of the molecular and cellular mechanisms of alcohol metabolism and aldehyde production in relation to human health. Understanding these processes is particularly relevant considering that over 560 million people in the world, being characterized by the presence of genetic variants associated with impaired alcohol metabolism and detoxification pathways, are more susceptible to aldehyde toxicity resulting in a significant increase of their overall cancer risk.

Publications

Baldari S, Manni I, Di Rocco G, Piaggio G and **Toietta G** (2022) *In vivo* evaluation of the effects of acute C2H6O exposure on cell proliferation. Submitted to *Cancers,* Special Issue entitled "Alcohol Use and Cancer Risk". Impact Factor 2019: 6.126

Baldari S, Manni I, Di Rocco G, Paolini F, Palermo B, Piaggio G and **Toietta G** (2021) Reduction of Cell Proliferation by Acute C_2H_6O Exposure. *Cancers* (Basel), 13(19):4999. doi: 10.3390/cancers13194999. PMID: 34638483

Di Rocco G, Baldari S, Pani G and **Toietta G** (2019) Stem cells under the influence of alcohol: effects of ethanol consumption on stem/progenitor cells. *Cellular and Molecular Life Sciences*, 76(2):231-244. doi: 10.1007/s00018-018-2931-8

Trivisonno A, Alexander RW, Baldari S, Cohen SR, Di Rocco G, Gentile P, Magalon G, Magalon J, Miller RB, Womack H and **Toietta G** (2019) Intraoperative strategies for minimal manipulation of autologous adipose tissue for cellular and tissue-based therapies. *Stem Cells Translational Medicine*, 8:1265-1271. doi: 10.1007/s00018-018-2931-8

Testing an Internet-based guided self-help intervention to reduce alcohol misuse and co-occurring depression symptoms in students: Take Care of You (2017) (EA 17 20)

Huizink A, Faculty of Behavioral and Movement Sciences, Vrije Universiteit Amsterdam, The Netherlands

In this project a program was developed and evaluated, for use on the internet or a smartphone, to help young people to reduce their alcohol consumption. In

particular, young people, such as students, drink a lot of alcohol, which can harm their health and future prospects.

In the early stage of the project, a group of young people were asked for their opinion about the proposed content of the program. Based on their feedback, the program was fine tuned and finalized. Online questionnaires for the study were developed. The final version includes a 6-week program aimed at developing low-risk drinking habits according to the Dutch drinking guidelines.

503 young people, who expressed the wish to reduce their alcohol drinking, were recruited to take part in the study. They undertook the baseline assessment and were randomized into either the intervention condition (Boozebuster app) or the control condition (psychoeducational module).

Data collection has been completed for the follow-up assessments. 386 (76.7%) have also completed the second assessment at 6 weeks, and 349 (69.4%) filled in the final online questionnaire after 3 months. These data are now being analyzed to assess the effectiveness of the application in reducing alcohol use. The first results show that there was a time effect, indicating that both the intervention condition and the control condition showed a reduction in alcohol use over time. Also, depression symptoms and perceived stress levels were reduced in both groups. However, the intervention condition was not more effective than the control condition. Further post-hoc analyses will be conducted to examine whether the subgroup of drinkers (heavy drinkers, binge drinkers) and participants with different levels of adherence to the intervention show different results.

The intermediate conclusion (March 2022) is that an online intervention for reduction of alcohol consumption among young people seems feasible and attractive, based on the higher-than-expected number of participants in the study. Self-guided mobile interventions based on a lifestyle approach might be an attractive approach for young adults due to their preference for self-reliance, healthy living, and increased perceived anonymity. Such interventions are yet under studied, and it is known that interventions addressing solely problem drinking are less appealing to young adults. Overall, the effectiveness of our intervention does not seem to exceed the effectiveness of a simple control condition, in which participants received a single module of psychoeducation. It may be that a group of participants with a higher risk profile (heavy drinkers or binge drinkers) may benefit more from the intervention. Further definitive conclusions on the feasibility and the effectiveness will be drawn once all data have been analyzed. If effective for the high risk group, this intervention could be an inexpensive and scalable public health intervention to improve drinking habits in young adults with a relative risky pattern of drinking behavior.

Publications

Boumparis N, Schulte MH, Kleiboer A, **Huizink A** and Riper H (2021) A Mobile Intervention to Promote Low-risk Drinking Habits in Young Adults: Protocol for A Randomized Controlled Trial. *JMIR Research Protocols,* 10(6): e29750

Investigating the role of long non-coding RNA in alcoholic liver disease (ALD). (2017) (EA 17 63)

Chokshi S, Foundation for Liver Research, London, UK

A major complication of alcoholic liver disease (ALD) is increased susceptibility to bacterial infection, which can lead to worsening of liver disease, organ failure and death. A 'leaky' gut and consequent bacterial translocation into the systemic circulation is a central driver of immune insufficiency in patients with ALD.

The mechanisms by which the gut is damaged in ALD and how bacterial translocation impairs anti-bacterial immunity have not been well understood to date. Genome-wide investigation of dysregulated functional pathways and whether certain regulatory pathways, such as long non-coding RNAs (lncRNAs), could act as therapeutic targets to restore gut barrier integrity and/or re-establish an effective state of anti-bacterial immunity has been the aim of this project.

LncRNAs do not encode proteins but can regulate the expression of protein-coding genes. They play crucial roles in orchestrating immune defences to bacterial pathogens. In this research genome-wide analysis of both coding and non- coding genes have been performed in intestinal tissue and immune cells from a cohort of 92 subjects with varying severity of alcoholic liver disease to determine which specific biological pathways and lncRNAs are altered in ALD, whether they can be used as diagnostic markers, and whether they could be suitable therapeutic targets to achieve immune recovery in patients.

The results identified significant alterations in intestinal cell adhesion pathways in patients with ALD, supporting the conclusion that ongoing gut barrier damage and compensatory—but inefficient—repair mechanisms are a feature of this condition. Altered cell adhesion pathways are also observed during the development of cancer, which might suggest that pre-cancerous transcriptional signatures are present in the gut of patients with alcohol-related cirrhosis, which may be important for screening purposes. Furthermore, 25 completely novel lncRNAs were identified amongst the top-most dysregulated patients with ALD, which may be important for the identification of novel diagnostic or therapeutic targets.

This study also identified specific immune-related transcriptional profiles associated with disease protection or progression to more severe stages of ALD, and functional pathway analysis will potentially define new diagnostic and therapeutic signatures associated with disease progression. This research provides a list of several novel molecular targets that may be used to rescue the immune suppressed state observed in advanced ALD patients. Restoration of efficient antibacterial immunity would significantly reduce mortality in these patients.

Publications

Ryan JM, Adams H, Tsou HL, Devshi D, Harris N, Sieh YX, Hadzhiolova T, Pavlova S, Fairclough S, Atkinson S, Tyson L, Wright G, Patel V, Evans A, Simonova M, Katzarov K, Shawcross DL, Bajaj J, Fagan A, McQuillin A, Thursz M, Morgan MY, Riva A and **Chokshi S** (submitted) Genetic variants of Interferon Lambda 4 are associated with susceptibility to bacterial infection in alcohol-related liver disease. *Gastroenterology*.

Biomarkers of subclinical ischemic damage and low-grade inflammation as possible mediators of association between alcohol intake and vascular risk (2017) (EA 17 67)

Costanzo S, Department of Epidemiology and Prevention Istituto Neurologico Mediterraneo NEUROMED, Pozzilli (IS), Italy

Moderate alcohol consumption is associated with lower risk of cardiovascular disease (CVD), while alcohol abuse has detrimental effects. The mediators of the association of alcohol consumption and CVD remain to be established. The aim of this project was to investigate the relation between alcohol consumption and biomarkers of ischemic damage and inflammation, and to study their possible role as the explanatory variable of the association between alcohol intake and CVD.
Analyses of the large general-population-based Moli-sani cohort (n=22,942 individuals), showed that alcohol consumption up to 70 grams/day (nadir 20 grams/day) was associated with a multivariable (adjusted for covariates) relative reduction in the risk of developing coronary events, in comparison with long-life abstainers (former drinkers have been considered apart and not included in the reference group). Intake of alcohol up to 55 grams/day was associated with a lower risk of total mortality. This group had 13% (95%CI: 1% to 23%) lower risk of coronary events in comparison with long-life abstainers.

Next the proportion of treatment effect mediated by 20 biomarkers was calculated. Lipids explained 38.3% of the association, with HDL and LP-a having a major role. Chronic subclinical inflammation explained 16.0% of the association (12.7% by C-reactive protein). Other biomarkers overall accounted for 57.7% (insulin, C-peptide, vitamin D and D-dimer as the major contributors). All the biomarkers considered explained up to 75.0%. However, most of them are correlated. So, a restricted panel formed by 7 main contributors for each category (HDL, LP-a, C-reactive protein, insulin, C-peptide, vitamin D and D-dimer) was able to explain up to 81.7%. However, all these calculations, despite the large sample size, are plagued by large statistical uncertainty, as illustrated by the wide 95% confidence intervals and P-values.

In conclusion, alcohol consumption up to 55 grams/day (nadir 20 grams/day) is associated with 13% reduced risk of coronary events. This association is explained by modulation of lipids by alcohol, chronic inflammation and other biomarkers of cardiovascular risk, although statistical uncertainty remains.

Publications

Caiano LM, **Costanzo S**, Panzera T, Di Castelnuovo A, de Gaetano G, Donati MB, Ageno W and Iacoviello L, on behalf of the Moli-sani Investigators (2021) Association between body mass index, waist circumference, and relative fat mass with the risk of first unprovoked venous thromboembolism. *Nutrition, Metabolism and Cardiovascular Diseases*. 31(11); 3122-3130. doi.org/10.1016/ j.numecd.2021.07.018

Dissecting the activation of liver-generated microglia and neuroinflammation during alcohol misuse (2018) (EA 18 14)

Cubero FJ Department of Immunology, Ophthalmology and ENT, Complutense University School of Medicine, Madrid, Spain

Alcohol misuse is a leading risk factor for ill-health worldwide, accounting for a considerable number of premature deaths per year. While an association between alcohol-related hepatic damage and brain inflammation has been suggested, the underlying mechanism is not fully understood. That is why this research focused on casual relationships between alcohol-derived hepatic injury and microglia activation and neuroinflammation using several experimental models of alcoholic liver disease. Results showed increased intestinal permeability, loss of zonula occludens-1 and

MUCIN-2 expression, and alterations in microbiota-increased *Lactobacillus* and decreased *Lachnospiraceae* species-were found in the large intestine of mice exposed to ethanol. Also, increased TUNEL-positive cells, infiltration of CD11b-positive immune cells, pro-inflammatory cytokines (e.g., tlr4, tnf, il1β), and markers of lipid accumulation were evident in livers of mice exposed to ethanol, particularly in females.

In conclusion, acute binge drinking triggers hepatic steatosis accompanied by minor elevations of liver transaminases. Moreover the results suggest that binge alcohol consumption might initiate monocyte infiltration in the brain. However, chronic alcohol drinking causes systemic inflammation, hepatic damage, cell death, compensatory proliferation and hepatic infiltration of leukocytes which is accompanied by fibrosis when binge drinking is present. These results are exacerbated in combination with a high fat diet Additionally gut leakage, liver inflammation and neuroinflammation are associated with the progression of the disease.

Publications

Chen C, Nelson LJ, Ávila MA and **Cubero FJ** (2019) Mitogen-Activated Protein Kinases (MAPKs) and Cholangiocarcinoma: The Missing Link. *Cells*, 8(10):1172. Published online 2019 Sep 28. doi: 10.3390/cells8101172

Cubero FJ (2019). Staging NAFLD: Diagnostic and Therapeutic Value of TAM Signaling. *Cellular and Molecular Gastroenterology and Hepatology,* pii: S2352-345X(19)30169-9. doi: 10.1016/j.jcmgh.2019.11.014

Cubero FJ, Woitok MM, Zoubek ME, de Bruin A, Hatting M and Trautwein C (2019). Disruption of the FasL/Fas axis protects against inflammation-derived tumorigenesis in chronic liver disease. *Cell Death and Disease,* 10(2):115. Published online 2019 Feb 8. doi: 10.1038/s41419-019-1391-x

Liao L, Schneider KM, Galvez EJC, Frissen M, Marschall HU, Su H, Hatting M, Wahlström A, Haybaeck J, Puchas P, Mohs A, Peng J, Bergheim I, Nier A, Hennings J, Reißing J, Zimmermann HW, Longerich T, Strowig T, Liedtke C and **Cubero FJ,** Trautwein C (2019). Intestinal dysbiosis augments liver disease progression via NLRP3 in a murine model of primary sclerosing cholangitis. *Gut,* 68(8):1477-1492. doi: 10.1136/gutjnl-2018-316670. Epub 2019 Mar 14

Manieri E, Herrera-Melle L, Mora A, Tomas-Loba A, Leiva-Vega L, Fernandez DI, Rodriguez E, Morán L, Hernández-Cosido L, Torres JL, Seoane LM, **Cubero FJ,** Marcos M and Sabio G (2019) Adiponectin accounts for gender differences in hepatocellular carcinoma incidence. *Journal of Experimental Medicine,* 216(5):1108–1119

Lamas-Paz A, Hao F, Nelson LJ, Vazquez MT, Canals S, Gomez Del Moral M, Martinez-Naves E, Nevzorova YA and **Cubero FJ** (2018). Alcoholic liver disease:

Utility of animal models. *World Journal of Gastroenterology,* 7;24(45):5063-5075. doi: 10.3748/wjg.v24.i45.5063

Theses and Awards
Dr. Cubero - ERAB Publications Award 2020

Using genome-wide polygenic scores to explain adolescents' drinking behaviours and their concurrent and subsequent health (2018) (EA 18 16)

Von Stumm S, Kings College London, London, UK. Now at Department of Education, University of York, UK

Adolescence is a critical period for experimenting with alcohol, and these early experiences have long-term influences on alcohol-related behaviours throughout adulthood. This project examined the utility of genome-wide polygenic scores (GPS) for predicting alcohol use during adolescence and young adulthood.
The researchers used GPS based on the Genome-wide association study and Sequencing Consortium of Alcohol and Nicotine use (GSCAN) study on drinks per week to predict alcohol use in a longitudinal, UK-representative sample of unrelated adolescents aged 16 through to 22 years (N_{max} = 3390).
The predictive validity of GPS for phenotypic alcohol use was evident in adolescence and increased in young adulthood. The findings suggest that GPS, which are available from birth, may be potentially useful for identifying individuals at risk for harmful and hazardous alcohol use. However, because the overall effect sizes were small, the utility of the GPS that are currently available is limited for the prediction of individual-level alcohol use.

Publications

Kandaswamy R, Allegrini A, Nancarrow A, Cave SN, Plomin R and **von Stumm S** (2021) Predicting alcohol use from genome-wide polygenic scores, environmental factors, and their interactions in young adulthood. *Psychosomatic Medicine*, August 31. doi: 10.1097/PSY.0000000000001005

Kandaswamy R, Allegrini A, Plomin R and **von Stumm S** (2021) Predictive validity of genome-wide polygenic scores for alcohol use from adolescence to young adulthood. *Drug Alcohol Dependence*, 219:108480. https://doi.org/10.1016/j.drugalcdep.2020.108480

The influence of alcohol-consumption-induced DNA methylation changes on lifestyle and health in the general population (2018) (EA 18 17)

Waldenberger M, Institute of Epidemiology, Helmholtz Zentrum München, Munich, Germany

In order to research the health effects of alcohol consumption, accurate measures of consumption are of great importance. The typical self-report questionnaires used in scientific studies are prone to bias, often by under-reporting. A reliable biomarker for alcohol use would be of benefit for both research into alcohol-related disease and clinical treatment. Knowing the precise effects of alcohol consumption on a molecular level would facilitate the advancement of medical interventions, particularly with regard to drug development, but also potentially in treating addiction.

In this project many molecular "signposts" of drinking behaviour – some changing as consumption changes – have been discovered and a subset of these signposts are also related to liver function. It remains to be fully determined if alcohol consumption acts through these signposts to cause disease, or if the signposts act only as indicators of drinking behaviour.

The research into validation of the existing biomarkers for alcohol consumption emphasizes both the need for better implementation of methodology in biomarker development, and the difficulty with standardization of methylation data processing. Noting the weaknesses pointed out by this publication should help future researchers be more on guard against these issues, thereby aiding in the discovery of a widely implementable, reliable clinical marker of alcohol consumption, one that is not affected by optimistic self-report or forms of recall bias.

Publications

Maas SCE, Vidaki A, Teumer A, de Oliveira Costeira R, Wilson R, van Dongen J, Beekman M, BIOS Consortium, Boomsma DI, Slagboom PE, van Heemst D, van der Kallen CJH, van den Berg LH, Kunze S, Ladwig K-H, **Waldenberger M**, Peters A, Bell JT, van Meurs JBJ, Uitterlinden AG, Voortman T, Ikram MA, Ghanbari M and Kayser

M (2021) Validation of biomarkers, models, and methodology for epigenetic inference of alcohol consumption from blood. *Clinical Epigenetics* 13, Article number: 198

Dugué PA, Wilson R, Lehne B, Jayasekara H, Wang X, Jung CH, Joo JE, Makalic E, Schmidt DF, Baglietto L, Severi G, Gieger C, Ladwig K-H, Peters A, Kooner JS, Southey MC, English DR, **Waldenberger M**, Chgambers JC,Giles GG and Milne RL (2021). Alcohol consumption is associated with widespread changes in blood DNA methylation: Analysis of cross-sectional and longitudinal data. *Addiction Biology*, 26(1): e12855. doi: 10.1111/adb.12855

Susceptibility to alcohol dependence, a role for the matricellular protein hevin. (2018) (EA 18 19)

Callado LF, Department of Pharmacology, University of the Basque Country Medical School, Leioa, Spain. Co-applicants: Vialou V and Erdozain AM

This research focused on a matricellular protein, hevin, expressed in neurons in the adult brain. Hevin has been implicated in synaptogenesis, the physiological regulation of mood, and in the regulation of the rewarding properties of drugs such as cocaine and, more recently, ethanol.

The research had several goals. The primary goal was to elucidate the role of hevin protein in alcoholism, by measuring and comparing its expression levels in postmortem human brain samples of alcoholic subjects, subjects with major depression, and controls. The researchers detected greater expression levels of hevin in the alcoholic group compared to controls in the prefrontal cortex, hippocampus and cerebellum. Interestingly, neither alcoholism nor depression groups showed significant differences in hevin expression in the caudate nucleus.

Another aim was to evaluate the effects of alcohol exposure on hevin levels in various brain regions and in the blood, using a mice model. They showed that hevin protein is decreased after an acute injection of alcohol in the prefrontal cortex and the amygdala. This suggests that hevin might be implicated in the emotional response to alcohol and in the motivation to drug taking. More importantly, hevin protein is increased in nucleus accumbens and dorsal striatum only in the alcohol relapse group, but not after acute or chronic alcohol injection. The nucleus accumbens plays an important role in several aspects of drug addiction. This result suggests that hevin participates in drug relapse.

To test the role of hevin in drug relapse, the researchers specifically downregulated hevin expression in nucleus accumbens astrocytes and evaluated the consequences

of such manipulation in alcohol consumption before and after withdrawal. Hevin downregulation induced a significant increase in consumption of high doses of alcohol before withdrawal as well as an increase in alcohol consumption after withdrawal, during relapse.
In conclusion, the protein hevin is overexpressed in the brain of subjects with alcoholism. The present results reinforce the hypothesis of hevin playing a role in alcohol dependence in humans.

Publications

Nuñez-del Moral A, Bianchi PC, Cruz FC, Vialou V, **Callado LF**, Erdozain AM (in preparation) Matricellular protein hevin brain expression is altered in chronic alcohol abusers and mice exposed to alcohol.

Nuñez-del Moral A, Brocos-Mosquera I, Vialou V, **Callado LF** and Erdozain AM (2021) Characterization of hevin (SPARCL1) immunoreactivity in postmortem human brain homogenates. Neuroscience, 467:91-109

Nuñez-del Moral A and **Callado LF** (2020) Alkohola edatearen eragina garun nerabean. *EKAIA EHUko Zientzia eta Teknologia aldizkaria*, (38)41-53.

Mongrédien R. Erdozain AM, Dumas S, Cutando L, Nuñez del Moral A, Puighermanal E, Amin SR, Giros B, Valjent E, Meana JJ, Gautron S, **Callado LF**, Fabre V and **Vialou V** (2019) Cartography of hevin-expressing cells in the adult brain reveals prominent expression in astrocytes and parvalbumin neurons. *Brain Structure and Function*, 224:1219-1244

How are alcohol consumption and beverage choices influenced by treatment factors and associated with psychosocial well-being in colorectal cancer survivors? (2018) (EA 18 20)

Mols F, Department of Medical and Clinical Psychology, Tilburg University, Tilburg, The Netherlands

This project focused on alcohol consumption and beverage choices and psychosocial well-being in colorectal cancer (CRC) survivors in the Netherlands.
The findings are that CRC survivors decreased their alcohol consumption in the two years post-diagnosis, although they still often drank heavy amounts of alcohol, regardless of their cancer. It was observed that there were more males with higher educational backgrounds, those who were more physically active or those

without a (permanent) stoma that consumed more alcohol in the first two years post-diagnosis.

Next, it was also observed that alcohol consumption was longitudinally related to less anxiety and depression and better Health-Related Quality of Life (HRQoL) in CRC survivors. This was mostly the case for consumption of beer and wine, and was more often found in men or younger persons (<67 years at baseline).

Furthermore, while former alcohol consumption was longitudinally associated with worse psychosocial outcomes, current drinking, particularly wine, was associated with less anxiety and depression and better HRQoL in CRC survivors within the first 15 years post-diagnosis.

It is important to consider that besides the potential negative effects of alcohol on patients' health, alcohol consumption (e.g. social or casual drinking) may at the same time be positively related with psychosocial outcomes. This could perhaps be due to the fact that CRC survivors slowly return to their social drinking habits, and are doing better in general. Future research should focus qualitatively on why cancer survivors consume alcohol or why they quit drinking.

Publications

Révész D, Bonhof CS, Bours MJL, Weijenberg MP, Vreugdenhil G, van de Poll-Franse LV and **Mols F** (under review). Sociodemographic, clinical, lifestyle and psychological correlates of peripheral neuropathy – a study among 2–12-year colorectal cancer survivors from the PROFILES registry.

Révész D, Bours MJL, Weijenberg MP and **Mols F** (2022) Longitudinal associations of former and current alcohol consumption with psychosocial outcomes among colorectal cancer survivors 1-15 years after diagnosis. Nutrition and Cancer, 2022 Feb 25;1-9.

Révész D, Bours MJL, Wegdam, Keulen ETP, Breukink SO, Slooter GD, Vogelaar FJ, Weijenberg MP and **Mols F** (2021) Associations between alcohol consumption and anxiety, depression, and health-related quality of life in colorectal cancer survivors. *Journal of Cancer Survivorship*, September 16. doi: 10.1007/s11764-021-01090-y

Révész D, Bours MJL, Wegdam JA, Keulen ETP, Breukink SO, Slooter GD, Vogelaar FJ, Weijenberg MP and **Mols F** (2021) Longitudinal associations of sociodemographic, lifestyle, and clinical factors with alcohol consumption in colorectal cancer survivors up to 2 years post diagnosis. *Supportive Care in Cancer*, 29(10):5935-5943. https://pubmed.ncbi.nlm.nih.gov/33761003/

Effect of beer consumption on microbiota: Can it protect from cognitive decline associated with Alzheimer's Disease or neurological damage? (2018) (EA 18 40)

Cannella N, School of Pharmacy, University of Camerino, Camerino, Italy

This project studied whether the pre/probiotic effects of beer are able to counteract cognitive decline associated with aging and development of Alzheimer's disease (AD)-like symptoms in a genetic model of AD.

Experiments using a rat model showed that beer consumption does not affect memory performance, which remained at the same level of equal-concentrated alcohol with the control group.

In experiments using mice the combination of beer and yeast increased the Novel-Object Recognition task. This suggests that the combination of beer + yeast is able to prevent the impairment of short-term memory in this murine model of AD. Finally, this project showed that the prebiotic and probiotic effects of beer + yeast reduce inflammation in the hippocampal and fronto-cortical region of AD mice.

Altogether, these findings suggest that consumption of beer-derived probiotics could ameliorate microbiome composition and reduce inflammation in brain areas associated with the development of AD; thereby decreasing the risk of developing the AD condition.

Publications

Gogoi O, Cecarini V, Bonfili L, D'Argenio V, Zheng Y, Masi A, Eleuteri AM and **Cannella N** (In preparation) Neuroprotective effects of unpasteurized beer in a mouse model of Alzheimer's disease Veronica Lunerti, Hongwu Li , Federica Benvenuti,

Shen Q, Domi A, Di Martino RMC, Bottegoni G, Haass-Koffler CL and **Cannella N** (in preparation) The multitarget FAAH inhibitor/D3 partial agonist ARN15381 decreases nicotine self-administration and seeking in rats. Addiction Biology.

Borruto AM, Domi A, Soverchia L, Domi E, Li H and **Cannella N** (2022) Preclinical Models of Relapse to Psychostimulants Induced by Environmental Stimuli. In: Aguilar M.A. (eds) Methods for Preclinical Research in Addiction. *Neuromethods*, vol 174. Humana, New York, NY. https://doi.org/10.1007/978-1-0716-1748-9_7

Haass-Koffler CL, **Cannella N** and Ciccocioppo R (2020). Translational dynamics of alcohol tolerance of preclinical models and human laboratory studies. *Experimental Clinical Psychopharmacology*, 28(4):417-425

The role of the circulating microbiome in determining outcome in patients with alcohol related liver disease (2018) (EA 18 58)

Dhanda A, Department of Hepatology, University of Plymouth, Plymouth, UK

Infection is one of the commonest causes of death in patients with alcohol-related liver disease. Its early identification will speed treatment and improve survival. The aim of this project was to identify biomarkers (fragments of bacterial or fungal DNA) in patient's serum that can be used to predict later infection or death.
The extraction of cell-free DNA from serum samples from patients with alcohol-related liver disease have been successfully optimised. DNA from the serum has been sequenced using the NovaSeq 6000 platform. Reads will now be mapped to a microbial gene catalog and bioinformatics analysis will be performed to detect gene families and functions associated with clinical outcomes.

Publications

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Comparing the bioactivities of the major human metabolites of hop-derived prenylated flavonoids to those of their parent compounds (2018) (EA 18 69)

Rychlik M, Department of Food and Nutritional Sciences, Technical University Munich, Munich, Germany

The aim of this project was to understand the health effects of known "in circulatory" metabolites of 6- and 8-prenylnaringenin (hop derived compounds), which might have a pharmaceutical potential in treating cancer and metabolic syndrome (obesity). In turn, this research aimed to help understand the bioactivities

of these compounds after absorption and metabolism (in-vivo) to deduce their health effects.
A new method for the sensitive analytical quantitation of the prenylated flavonoids in beer, hops and tea was developed. For the first time xanthohumol-C and isoxanthohumol-C could be quantified in beer. Furthermore, the metabolites of these compounds were synthesized to be able to evaluate the bioactivities of prenylated flavonoids. This resulted in tentative evidence that the hydroxylation and glucuronidation of the prenylated flavonoids in the body might even increase their effects on health. This may be especially important in glucose transport and metabolic syndrome activities, which intertwines with cancer cells, as prenylated flavonoids possibly slow down cell uptake of sugars, an important factor in tumour growth.
Further research is required before a definite conclusion on the bioactivities of these new synthesised compounds could be established.

Publications

Buckett L, Schönberger S, Spindler V, Sus N, Frank J , Frank O and **Rychlik M** (2022) Synthesis of human phase I and phase II metabolites of hop (Humulus lupulus) prenylated flavonoids. *Metabolites* (open access)

Buckett L, Schinko S, Urmann C., Riepl H and **Rychlik M** (2020). Stable Isotope Dilution Analysis of the Major Prenylated Flavonoids Found in Beer, Hop Tea, and Hops. *Frontiers in Nutrition*, 7:619921

Theses and Awards

Dr. Lance Buckett – PhD 2022

Analysis of the synergistic anti-inflammatory effect of the hop derived beer compounds iso-alpha-acids and xanthohumol (2018) (EEP 18 07)

Hellebrand C, Institute of Biochemistry, Friedrich-Alexander-University, Erlangen-Nürenberg, Germany and Bergheim I, Department of Nutritional Sciences, University of Vienna, Austria

World-wide, and especially in Germany and Austria, beer is still among the most frequently consumed alcoholic drinks. Epidemiological and animal studies suggest that chronic consumption of hard spirits might be more harmful for the liver and probably other organs than that of fermented alcoholic beverages. However,

mechanisms underlying the different effects of alcoholic beverages have not yet been fully understood.

Beer contains large amounts of secondary plant compounds as hops are a key compound in the brewing process. Among them, iso-alpha-acids and xanthohumol have been shown to be among those readily taken up in a dose-dependent manner within in the first hours of (beer) consumption. Previous studies reported that both compounds exhibit numerous health beneficial effects including anti-inflammatory and even anti-fibrotic effects. However, doses of iso-alpha-acids and xanthohumol used in these studies were mostly way beyond those taken in when consuming beer in moderate amounts. Also, in these studies, researchers did not study the combination of both substances together, as would be found in beer or other hop containing foods and beverages.

The first aim of the project was to study the anti-fibrotic effects of the combination of iso-alpha-acids and xanthohumol on primary human liver cells, called hepatic stellate cells. Upon activation, these liver cells secrete proteins that form the scar tissue. Results show that a combination of very low doses of both iso-alpha-acids and xanthohumol inhibits the activation process as well as the proliferation and production of pro-fibrogenic proteins. Interestingly, the same (low) doses of the compounds alone showed no significant effects, indicating that the compounds synergistically inhibit different pro-fibrogenic processes.

The second aim was to analyze the anti-inflammatory effects of iso-alpha-acids and xanthohumol in doses equivalent to moderate beer consumption. A single-blind, placebo-controlled crossover designed study was performed in healthy, normal weight young adults to assess the effects of low doses of the two compounds, separate and together, on the inflammatory response of peripheral blood mononuclear cells. Key findings included that the acute intake of low doses of both compounds or a combined intake of the two compounds attenuate the inflammatory response resulting from bacterial toxins.

In conclusion, this project revealed that the hop derived compounds iso-alpha-acids and xanthohumol show synergistic health beneficial effects in preclinical models of liver injury and on the immune responses in humans.

Publications

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Annexes

Annex 1: Structure of the Boards

ERAB was founded with two Boards. The Board of Directors acts as guarantor for the independence of the research promoted by the Advisory Board.

1. The Board of Directors included: businessmen, personalities of civil society and the academic world, and representatives of brewers and trade associations. However, the by-laws insisted on a **majority of public members** (trustees). The Board had the widest powers to perform all acts of management and disposal, directly or indirectly.

   The Advisory Board advised the Board of Directors on which grant applications should be funded.

   The following have served as members of the Board of Directors between 2004 and 2022:

   - Mr. Paul **Bergqvist** - Former President of The Brewers of Europe, Denmark. (Industry Member 2004 - 2006).
   - Professor Daniel **Bessa** - Accountant, Portugal. (Public Member 2007 - 2018).
   - Mrs. Sarah **Boselli-Lee** - Heineken, The Netherlands. (Industry Member 2016 - 2018).
   - Frau Edeltraud **Böhm-Amtmann** - Formerly of the Representation of Bavaria to the EU. (Public Member 2004 - 2007).
   - Mr. Demetrio **Carceller** - Former President of The Brewers of Europe, Spain. (Industry Member 2013 - 2016).
   - Baron Daniel **Cardon de Lichtbuer** - Formerly with Child Focus Europe, Belgium. (Public Member 2004 - 2007).
   - Professor Christopher P. **Day** - Vice-chancellor and President, University of Newcastle-upon-Tyne, UK. (Ex-officio Public Member 2016 - 2022).
   - Mr. Alberto **da Ponte** - Former President of The Brewers of Europe, Portugal. (Industry Member 2008 - 2012).
   - Countess Antoinette **d'Aspremont Lynden** - Political Science Institute in Lille, France. (Public Member 2016 - 2018).
   - Count Rodolphe **de Looz Corswarem** - President of European Historic Houses Association. (Honorary Member 2010 - 2011, Public Member 2011 - 2018).
   - Emeritus Professor Philippe **De Witte** - Université Catholique de Louvain-la-Neuve, Belgium. (Ex-officio Public Member 2007 - 2016).

- Mr. Markus **Ferber** - MEP, Germany. Public Member (2010 - 2016).
- Mr. Raymond **Georis** - Former Chairman of the Madariaga European Foundation, Belgium. (**Founder Member**) (Public Member and Chairman 2004 - 2010, Honorary Member 2009 - 2010, Public Member and Chairman 2015 - 2016).
- Mr. Rutger **Goethart** - Heineken, The Netherlands. (Industry Member 2008 - 2012).
- Mme. Véronique **Guérin** - Managing Director of the Bureau Européen de l'Agriculture Française, France. (Public Member 2016 - 2018).
- Mr. Simon **Jackson** - Formerly CEO of the Institute of Brewing and Distilling, UK. (Industry Member 2009 - 2018).
- Emeritus Professor Oliver F. W. **James** - Former pro-vice Chancellor, University of Newcastle, UK. (**Founder Member**) (Ex-officio Public Member 2004 - 2006, Honorary Member 2006 - 2009, Public Member and Chairman 2009 - 2015).
- Mr. Morten Georg **Jensen** - Carlsberg Group, Denmark. (Industry Member 2013 - 2016, Public Member 2017 - 2018).
- Emeritus Professor Frans J. **Kok** - Formerly Professor of Human Nutrition, Wageningen University, The Netherlands. (Public Member and Chairman 2016 - 2022).
- Dr. Isak **Lindstedt** - General Practitioner, Sweden. (Public Member 2016 - 2018).
- Dr. David **Long** MBE - Consultant, Former Director, Brewing, British Beer & Pub Association, UK. (Industry Member 2004 - 2009, Honorary Member 2009 - 2018).
- Mr. Jean **Martin** - Former President of the European Confederation of the Food & Drink Industry. (Public Member 2004 - 2018).
- Dr. Mack C **Mitchell** Jr. - ABMRF, USA. (Public Member 2004 - 2015).
- Mr. Knud Hedeager **Nielsen** - Carlsberg Group, Denmark. (Industry Member 2006 - 2012).
- Mr. Morten **Nielsen** - Carlsberg Group, Denmark. (Industry Member 2012 - 2013).
- Miss Johanna **Nyman** - President of the European Youth Forum, Finland. (Public Member 2016 - 2018).
- Mr. Jacobo **Olalla Marañón** - Cerveceros de España, Spain. (Industry Member 2004 - 2018).
- Mr. Pavlos **Photiades** - President of The Brewers of Europe, Cyprus. (Industry Member 2016 - 2022).
- Mr. Piero **Perron** - Former President of The Brewers of Europe. (**Founder Member**). (Public Member 2004 - 2006, Honorary Member 2006 - 2018).

- Mrs. Heidrun **Piwernetz** - Formerly of the Representation of Bavaria to the EU. (Public Member 2007 - 2010).
- Mr. Artur **Santos Silva** - Formerly with the Portuguese Bank of Investment, Portugal. (Public Member 2004 - 2007).
- Mr. Kieran **Simpson** - Formerly with Heineken, The Netherlands. (Industry Member 2004 - 2008 and 2012 - 2016).
- Dr. Erik **Skovenborg** - Medical Doctor, Denmark. (Public Member 2004 - 2016).
- Emeritus Professor Richard **Smallwood** - Former Commonwealth Chief Medical Officer (1999-2003), Australia. (Honorary Member 2004 - 2018).
- Dr. Renate **Sommer** - MEP, Germany. (Public Member 2016 - 2018).
- Mr. Ulf **Spendrup** - Former President of The Brewers of Europe, Sweden. (Industry Member 2006 - 2008).
- Mr. Eric **Vaes** - Formerly with InBev, Belgium. (Industry Member 2004 - 2006).
- Mrs. Janet **Witheridge** - ERAB Secretary-General, UK. (Ex-officio Public Member 2009 - 2022).
- Ms. Vanessa **Witkowski**. Belgium. (Public Member 2008 - 2011).

2. The Advisory Board was composed of specialists in the behavioural and biomedical sciences, with a proven international, independent, scientific stature, and from a variety of countries. Their role was to examine the applications, suggest peer reviewers, and recommend to the Board of Directors which applications should be funded.

   The following have served as members of the ERAB Advisory Board between 2003 and 2022:

   - Professor Giovanni **Addolorato** - Università Cattolica del Sacro Cuore, Rome, Italy. (2006 - 2022).
   - Associate Professor Bridgette M. **Bewick** - University of Leeds, UK. (2015 - 2022).
   - Dr. Marie **Choquet** - INSERM, France. (2003 - 2005).
   - Professor Christopher P **Day** - University of Newcastle-upon-Tyne, UK. (2003 - 2016), **Chairman** (2016 - 2022).
   - Emeritus Professor Philippe **De Witte** - University of Louvain la Neuve, Belgium. (2003 -2016) Chairman (2006 - 2016).
   - Professor Juan **Díez Nicolás** - Complutense University of Madrid, Spain. (2003 - 2005).

- Associate Professor Ramon **Estruch** - University of Barcelona, Spain. (2011 - 2022).
- Professor Antonio **Gasbarrini** - Catholic University of Rome, Italy. (2003 - 2006).
- Professor Oliver F W **James** - University of Newcastle upon Tyne, UK. (Chairman 2003 - 2006).
- Professor Wolfgang **Koenig** - University of Munich, Germany. (2003 - 2022).
- Associate Professor Marianne **Nissen Lund** - University of Copenhagen, Denmark. (2015 - 2022).
- Dr. Kari **Poikolainen** - Finnish Foundation for Alcohol Studies, Helsinki, Finland. (2006 - 2010).
- Professor Pekka **Sulkunen** - University of Helsinki, Finland. (2010 - 2015).
- Professor Piet A **van den Brandt** - Maastricht University, The Netherlands. (2003 - 2006).
- Dr. Dr. Sascha **Venturelli** - Eberhard Karls University Tuebingen, Germany. (2015 - 2022).
- Professor Matty P **Weijenberg** - Maastricht University, The Netherlands. (2007 - 2018).

Annex 2: IMAG Conferences

39th	2018	Leuven, Belgium	**ERAB/EU**
38th	2014	Amsterdam, The Netherlands	**ERAB/EU**
37th	2011	Montreal, Quebec, Canada	ABMRF/Canada
36th	2010	Frascati, Italy	**ERAB/EU**
35th	2007	Halifax, Nova Scotia, Canada	ABMRF/Canada
34th	2006	Copenhagen, Denmark	**ERAB/EU**
33rd	2005	Chicago, Illinois, USA	ABMRF/USA
32nd	2004	Canberra, ACT, Australia	AG/Australia and New Zealand
31st	2003	Niagara on the Lake, Ontario, Canada	ABMRF/Canada
30th	2002	Brussels, Belgium	MAG/UK
29th	2000	San Francisco, California, USA	ABMRF/USA
28th	1999	Melbourne, Victoria, Australia	MAG/Australia and New Zealand
27th	1998	Vancouver, BC, Canada	ABMRF/Canada
26th	1997	Bath, Somerset, UK	MAG/UK
25th	1996	Tucson, Arizona, USA	ABMRF/USA
24th	1995	Sydney, New South Wales, Australia	MAG/Australia and New Zealand
23rd	1994	Quebec, Canada	ABMRF/Canada
22nd	1993	London, UK	MAG/UK
21st	1992	La Jolla, California, USA	ABMRF/USA
20th	1991	Brisbane, Queensland, Australia	MAG/Australia and New Zealand

19th	1990	Jasper, Alberta, Canada	ABMRF/Canada
18th	1989	Eastbourne, Sussex, England	MAG/UK
17th	1988	Charleston, South Carolina, USA	ABMRF/USA
16th	1987	Melbourne, Victoria, Australia	MAG/Australia and New Zealand
15th	1986	Ottawa, Ontario, Canada	ABMRF/Canada
14th	1985	Turnberry, South Ayrshire, Scotland	MAG/UK
13th	1984	Cambridge, Massachusetts, USA	ABMRF/USA
12th	1983	Sydney, New South Wales, Australia	MAG/Australia and New Zealand
11th	1982	Halifax, Nova Scotia, Canada	ABMRF/Canada
10th	1981	Stratford-Upon-Avon, Warwicks, England	MAG/UK
9th	1980	Washington, DC, USA	ABMRF/USA
8th	1979	Melbourne, Victoria, Australia	MAG/Australia and New Zealand
7th	1978	Toronto, Ontario, Canada	ABMRF/Canada
6th	1977	London, England	MAG/UK
5th	1976	Rosslyn, Virginia, USA	ABMRF/USA
4th	1975	Victoria, BC, Canada	ABMRF/Canada
3rd	1974	London, England	MAG/UK
2nd	1973	Hamilton, Bermuda	
1st	1972	Montebello, Quebec, Canada	

Annex 3: Awards and Collaborations

Travel and Exchange awards to encourage younger researchers in the field of alcohol research were made available as soon as the Foundation opened. Awards were open to European researchers under the age of 35 working in the field of alcohol research.

Travel awards were intended to facilitate conference participation by young researchers and were dependent on having an abstract accepted at the conference. Over 15 years, 83 travel awards were funded from 108 applications for a total of **€62,784**. They allowed participation in America, Australia and Europe.

Exchange awards were intended to facilitate visits by young researchers to laboratories / groups specialising in alcohol related research. They encouraged young researchers to gain expertise or exchange information. In the same period ERAB funded 15 of these more substantial exchange awards from 19 applications for a total of **€29,500**. The most popular destination was America but Australia, Canada and centres of excellence in Europe were also funded. Several resulted in publications which acknowledged ERAB funding.

Thesis Awards were first offered In 2011, providing small awards to assist in the cost of publication of theses covering alcohol related research. Over 8 years help was provided to publish 9 theses for a total of **€4,108**.

The Publications Award was launched in 2012, to acknowledge the outstanding scientific contribution made by some of its grantees. This award was for any former ERAB grantees who had had five or more papers, of three or more pages, published in peer reviewed journals with an acknowledgement of the funding received from ERAB. Since then, 20 awards have been made to just some of the eligible grantees for a total of **€20,000**.

The Lifetime Achievement Award marked ERAB's first 10 years. ERAB asked for nominations for this award. 7 excellent nominations were received, from Europe, Japan and the USA and the final decision as to who should receive the award was very difficult. The Advisory Board's decision was that the recipient should be Professor Gianluigi GESSA, Professor Emeritus at the University of Cagliari. His award was **€20,000** and this was announced at the International Meeting on Alcohol and Global Health (IMAG) Conference in Amsterdam in October

2014. His scientific career spanned more than 50 years and has made him an internationally recognized innovator and leader of modern "alcohology"

Collaborations

ERAB is proud of its collaboration with the European Society for Biomedical Research on alcohol (ESBRA) biennial Congress. In 2005, ERAB sponsored 4 travel awards for the leading young presenters at the conference in Canterbury, UK. In 2007, ERAB sponsored a keynote speaker and 4 travel awards for the conference in Berlin, Germany and in 2008, in Cagliari, Italy (**€8,000**).

ERAB was pleased to collaborate with the organisers of the "Alcoholism and Stress: A Framework for Future Treatment Strategies" conferences held in 2011, 2014 and 2017 and funded travel awards for 5 participants for each conference (**€6,776**).

ERAB also collaborated with the International Osteoporosis Foundation (IOF) and the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) to fund a joint scholarship for a researcher to attend the WCO-IOF-ESCEO congress in Krakow in 2018 (**€1,000**).

A further collaboration linked the website of the European Academy of Neurology with the ERAB website with a banner.

Annex 4: ERAB Publications

New Frontiers in Alcohol and Health Professor Philippe De Witte (Ed) (2010).

This book was published to mark ERAB's first seven years. There are five main chapters written by members of the ERAB Advisory Board. Each presented the research funded by ERAB with its added value in the context of the body of knowledge in that area.

The ERAB Board Members 2010 (from left to right): Professor Kari Poikolainen, Professor Giovanni Addolorato, Professor Wolfgang Koenig, Professor Phillipe De Witte, Professor Matty Weijenberg, Professor Chris Day with Janet Witheridge (ERAB Secretary-General) centre.

Some key points:

Introduction - Philippe De Witte (Université catholique de Louvain - Belgium - BE).

- This book reflects the harmonious relationship between the academic world and the European brewing industry. Despite the fact that they appear to be driven by divergent perspectives, they both agree that ignorance may lead to prejudice.
- To balance the beneficial effects in terms of cardiovascular disease and the detrimental effects, for example, in terms of cancer, alcohol consumption must be evaluated personally taking into account the contextual environment, the global body state and the consensual pleasure arising from its consumption.

Preface - Mack C Mitchell Jr. and Oliver FW James.

- Understanding the effects of alcohol on human health and behaviour is a matter of importance to all members of society.

Heavy alcohol intake episodes: determinants and interventions - Kari Poikolainen (Finnish Foundation for Alcohol Studies - Helsinki - FI).

- Occasional binges increase the risk of acute social and health problems while frequent episodes add to this the increased risk of chronic disease.
- The frequency of binges can sometimes be a better predictor of harm than long-term average intake.
- Approaches to reducing harm include brief interventions to reduce alcohol intake and reducing risk factors.
- Risk factors may grow out of both genetic and environmental factors and their interplay.
- Heavy alcohol intake episodes in the offspring are clearly related to parental heavy drinking as well as externalizing and internalizing problems.

Alcohol and the risk of cancer - Matty Weijenberg (Dept. of Epidemiology - Maastricht University - NL).

- Moderate alcohol consumption is associated with reduced risks of cardiovascular disease but may also increase the risk of several types of cancer, in particular cancers of the head and neck, oesophagus, colorectum and breast.
- Upon ingestion, alcohol is absorbed from the small intestine and taken up into the blood from where it is rapidly distributed over all organs and body fluids. Enzymes metabolise (convert) the alcohol first into acetaldehyde, a highly reactive, toxic and carcinogenic metabolite (substance), and then to ALDH, a less active substance that is further degraded to water and carbon dioxide for elimination. Genetic variations lead to different rates of metabolism.
- The formation of acetaldehyde in alcohol metabolism, and the results of experimental studies in animals and observational studies in humans, have led to the classification of both alcoholic beverages and ethanol in alcoholic beverages as group 1 mixture and agent, respectively, being carcinogenic to humans by the International Agency for Research on Cancer (IARC) in 2007.
- The exact mechanisms by which alcohol invokes the carcinogenic process are still not fully understood and probably differ by target organ. For example, the relationship with breast cancer may be associated with higher blood oestrogen levels and the synergistic effect of smoking and alcohol consumption may be due to alcohol acting as a solvent for other carcinogens.

Alcoholic liver disease - Chris P Day (Institute of Cellular Medicine - Newcastle University - UK).

- It is likely that humans have been consuming alcohol in excess since the Stone Age and the ancient Greeks made the link between alcohol and liver damage.

- Alcoholic liver disease is currently the most common cause of liver disease in the western world and ranges from fatty liver (steatosis) through alcoholic steatohepatitis to fibrosis, cirrhosis and hepatocellular carcinoma.
- End stage liver disease is the result of prolonged heavy alcohol intake in only a small proportion of drinkers.
- Obesity increases the risk of all stages of liver disease in heavy drinkers and genetic factors also contribute to an increased risk.
- Treatments for alcohol dependent patients aim to reduce consumption preferably to zero. Measures include psychological treatments, for example, brief interventions have been shown to significantly increase the chances of heavy drinkers moderating their drinking, and pharmacological treatments, for example, drugs can reduce alcohol craving.

Alcohol and its effects on cardiovascular system - Wolfgang Koenig (Dept of Internal Medicine II - Cardiology - Ulm University - DE).

- There is substantial experimental, clinical, and epidemiological evidence that moderate consumption of alcohol, through various mechanisms may beneficially affect cardiovascular health. The main mechanisms include anti-inflammatory effects, an increase in HDL cholesterol, and anti-thrombotic effects.
- The evidence suggests a causal link between moderate alcohol consumption, and its effects on the immune system and cardiovascular disease morbidity and mortality.
- More recent data from experimental studies further suggest that anti-apoptotic, anti-proliferative, and anti-migratory effects might also play a role, possibly mediated by polyphenols contained in various alcoholic beverages including beer and wine.
- Essential fatty acids like omega-3 fatty acids have also been shown to be increased by moderate amounts of alcohol and several studies are in support of a beneficial effect of increased circulatory levels of these compounds.
- Excessive alcohol consumption is certainly associated with adverse effects on the cardiovascular system as well as on many other organs in the body.

Brain, behaviour, genetic findings and pharmacological treatment in alcohol dependence - Giovanni Addolorato (Alcoholism Treatment Unit, Catholic University Rome - IT).

- To date, only three medications have been approved for treating alcohol dependent individuals, namely disulfiram, naltrexone and acamprosate. Their efficacy is modest and the results published in the literature have been, in some cases, inconsistent or even controversial.

- Pharmacotherapies are moving towards the discovery and development of treatment strategies that maximize a medication's alcohol deterrent effect and prolong periods of abstinence in alcohol dependent individuals.
- Genetic components play an important role and there is strong evidence that alcoholism runs in families.
- The rapid advancement of genetic knowledge provides an important opportunity to move towards a significant understanding of the contribution genes have to the development of alcohol dependence.

Endorsement - Professor TK Li, Former Chairman of Scientific Advisory Council of ABMRF, Former Director of NIAAA, NIH (USA).

"In today's world, we seek to understand, through scientific inquiry, why people drink, why some drink more than others, and why some drink despite negative consequences. Such scientific inquiries require the exploration of multiple spheres of influence ranging from genetic susceptibility to environmental risk within the context of prevailing socio-cultural norms. To this end, ERAB: The European Foundation for Alcohol Research is an outstanding example of how the brewing industry and academia are working together to address these issues of mutual concern in contemporary European societies."

The book is available as an e-book and a short leaflet on www.erab.org.

Underage Drinking: A Report on Drinking in the Second Decade of Life - Professor Philippe De Witte and Dr. Mack C Mitchell Jr. (Eds) (2012).

The complexity and importance of underage drinking prompted ERAB: The European Foundation for Alcohol Research (ERAB) in partnership with the ABMRF/ The Foundation for Alcohol Research (ABMRF) to initiate a state-of-the-art review. This report documented a collaborative project on underage drinking undertaken by experts in the field, in the EU and North America and was subject to peer review.

The project explored the extent of underage drinking and drew comparisons between both Continents. It reviewed the evidence on risk and protective factors as well as prevention and effective interventions in different situations. Its overall goal was to develop a set of recommendations that could be used by public health departments and key stakeholders in the individual countries that make up Europe and the United States and Canada.

While it was clear that a single solution to this problem could not be identified, given the different cultural backgrounds it provided a menu of effective strategies and made recommendations on the best method for applying them and the different cultural settings in which they had been shown to be effective.

It made clear that preventing risky drinking requires understanding of the important influence of family and peers and the recognition that some genetic traits like impulsivity, anxiety, sensation seeking and emotional dysregulation can also influence harmful drinking. These aspects (family and peers and genetic influence) are affected by cultural and environmental influences which, in turn, can influence each other. It concluded that a number of strategies are effective in some circumstances and warrant further study in different populations.

The Report is available as an e-book and a short leaflet on www.erab.org.

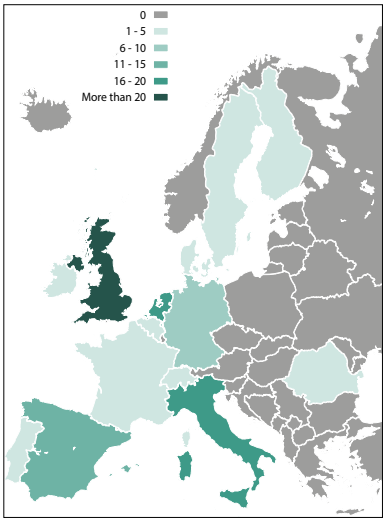
Editors and Authors

Franca Beccaria, Italy, EU - Mack C. Mitchell, Jr. (Ed), USA - Sherry H. Stewart, Canada - Philippe De Witte (Ed), Belgium, EU - Reinout W. Wiers, The Netherlands (EU) - Helene R. White, (Chair), USA - Antti Latvala, Finland, EU - Kim Fromme, USA - Patricia J. Conrod, Canada (from left to right in the photograph)

Annex 5: Key Statistics: 2003 - 2022

Total subscriptions 2003 to 2022	€ 8,430,699
Total grant spend 2003 to 2022	€ 7,747,427

Total Applications including all pre-proposals from 2017	731	
Total Applications Funded	102	
Total grants funded but not completed	2	
Of the grants funded:	-	
· number of two-year grants	81	
· number of biomedical grants	69	
· number of psychosocial grants	36	
· number of publications citing ERAB	317	
Travel Award Applications (Funded)	108	(82)
Exchange Award Applications (Funded)	18	(15)
Thesis Award Applications (Funded)	9	(9)
Publications Award Applications (Funded)	20	(20)



To date, ERAB funded projects have been undertaken in 14 different EU countries: - Belgium; Denmark; Finland; France; Germany; Ireland; Italy; The Netherlands; Portugal; Romania; Spain; Sweden; Switzerland and the UK.

Annex 6: Grantee Publications

Recipients of grants from ERAB: The European Foundation for Alcohol Research were asked to acknowledge ERAB funding in relevant publications and were expected to publish at least two papers from each project.

The final average was over 3 peer-reviewed publications per grant.

Of the 317 publications listed below 50% had an Impact Factor / Score above 4.0

Scientific Publications (updated August 2021)

Journal	Qty	I.F. 2020	I.S. 2020
ACR North American Advances	1	/	/
Acta Espanolas de Psiquiatria	1	/	1.20
Acta Psychiatrica Scandinavica	1	6.39	4.57
Addiction	9	6.53	3.69
Addiction Biology	14	4.28	3.65
Addiction Research and Theory	2	2.34	2.09
Addictive Behaviors	4	/	3.56
Addictive Behaviors Reports	1	/	3.30
Alcohol	10	/	2.06
Alcohol and Alcoholism	17	2.83	2.13
Alcoholism: Clinical and Experimental Research	15	3.46	2.82
Alimentary Pharmacology and Therapeutics	1	8.17	3.56
American Journal of Cardiology	1	2.78	2.26
American Journal of Clinical Nutrition	1	7.05	5.02
American Journal of Drug and Alcohol Abuse	2	3.83	3.15
American Journal of Psychiatry	1	18.11	6.91
American Journal of Physiology - Gastrointestinal and Liver Physiology	1	4.05	3.71
Analytical Chemistry	1	6.99	6.66
Annals of Internal Medicine	1	25.39	3.24
Annals of Nutrition and Metabolism	1	3.37	2.53
Annals of Oncology	1	32.98	11.13

Journal	Qty	I.F. 2020	I.S. 2020
Annals of the Romanian Society for Cell Biology	1	/	0.90
Atherosclerosis	2	5.16	3.70
Best Practice & Research Clinical Gastroenterology	1	/	2.75
Beverages	1	/	/
Biochemical Pharmacology	1	5.86	5.29
Biological Psychology	2	3.25	3.19
Biology	1	/	5.01
Biomedicines	1	/	5.61
BMC Complementary Medicine and Therapies	1	/	3.47
BMC Pediatrics	1	2.13	2.03
BMC Public Health	5	3.30	3.18
BMJ open	2	/	3.16
Brain Research	1	3.25	2.95
Brain, Behavior, and Immunity	2	7.22	5.79
Brain Connectivity	1	/	2.09
Brain Structure and Function	1	/	3.18
British Journal of Health Psychology	2	3.31	2.90
British Journal of Nutrition	2	3.72	3.28
British Journal of Pharmacology	2	8.74	7.73
Bulletin UASVM Food Science and Technology	3	/	/
Cellular and Molecular Life Sciences	1	9.26	8.46
Cancer Epidemiology, Biomarkers & Prevention	1	4.25	3.61
Cancers	1	5.97	6.10
Carcinogenesis	2	4.94	4.10
Cell Death and Disease	1	8.47	7.57
Cells	1	6.28	4.33
Cellular and Molecular Gastroenterology and Hepatology	1	/	5.03
Cellular Physiology and Biochemistry	2	/	5.14
Circulation	1	29.69	9.48
Clinical Epigenetics	1	/	6.03
Comprehensive Psychiatry	1	3.74	3.41
Critical Reviews in Food Science and Nutrition	1	11.18	9.98
Current Addiction Reports	2	/	2.85
Current Pharmaceutical Design	2	3.12	2.63

Journal	Qty	I.F. 2020	I.S. 2020
Diabetes and Vascular Disease Research	1	3.29	2.68
Data in Brief	1	/	1.13
Diabetes Care	1	19.11	11.38
Drug and Alcohol Dependence	4	/	4.07
Drug and Alcohol Review	2	2.47	2.35
Drug News and Perspectives	1	/	/
Drugs: Education, Prevention and Policy	2	1.71	1.77
EKAIA EHUko Zientzia eta Teknologia aldizkaria	1	/	/
Epidemiology	1	4.82	2.88
Epigenomics	1	4.78	4.06
European Journal of Cancer Prevention	2	2.50	1.95
European Journal of Clinical Investigation	1	4.69	3.80
European Journal of Clinical Nutrition	2	4.02	3.44
European Journal of Gastroenterology and Hepatology	1	2.57	2.05
European Journal of Neuroscience	1	3.39	2.94
European Journal of Pharmacology	1	4.43	4.12
European Journal of Pharmaceutical Sciences	1	4.38	4.23
European Psychiatry	1	5.36	4.44
European Journal of Public Health	2	3.37	2.43
European Neuropsychopharmacology	3	4.60	3.85
Experimental and Clinical Psychopharmacology	1	3.16	2.52
Food Analytical Methods	1	3.37	3.16
Food and Function	1	5.40	4.94
Food Chemistry	2	7.51	7.27
Fortschritte der Neurologie Psychiatrie	1	0.75	0.35
Frontiers in Behavioral Neuroscience	2	3.56	3.31
Frontiers in Bioscience - Landmark	1	4.01	3.89
Frontiers in Cellular Neuroscience	1	5.51	4.86
Frontiers in Molecular Neuroscience	2	/	5.13
Frontiers in Nutrition	1	/	5.87
Frontiers in Psychiatry	2	/	3.82
Frontiers in Psychology	1	2.99	2.78
Gastroenterology	3	22.68	7.34
Growth Factors	1	2.51	2.29

Journal	Qty	I.F. 2020	I.S. 2020
Gut	1	23.06	12.78
Health Psychology and Behavioral Medicine	1	/	1.40
Hepatology	4	17.43	9.04
Hepatology International	1	6.05	4.55
Hippocampus	1	3.90	3.46
Human Psychopharmacology: Clinical and Experimental	1	/	1.67
International Journal of Behavioral Medicine	1	2.23	2.01
International Journal of Cancer	2	7.40	6.27
International Journal of Food Sciences and Nutrition	1	3.83	2.84
International Journal of Intercultural Relations	2	/	2.52
International Journal of Oncology	1	5.65	5.24
International Journal of Neuropsychopharmacology	1	5.18	4.81
JAMA Psychiatry	1	21.60	8.16
Journal of Adolescent Health	2	5.01	3.26
Journal of Alcoholism & Drug Dependence	3	/	/
Journal of the American College of Cardiology	2	24.09	7.44
Journal of the American Society of Brewing Chemists	1	/	1.78
Journal of Behavioral and Brain Science	1	/	0.65
Journal of Biological Rhythms	1	3.18	2.96
Journal of Cancer Survivorship	1	/	3.82
Journal of Cellular Biochemistry	3	4.43	3.99
Journal of Clinical Investigation	1	14.81	10.27
Journal of Child Psychology and Psychiatry	1	8.98	6.47
Journal of Experimental Medicine	1	14.31	10.94
Journal of Food Science	1	3.17	2.90
Journal of Gastroenterology and Hepatology	1	4.03	1.50
Journal of Health Psychology	1	3.23	2.33
Journal of Hepatology	1	25.83	9.66
Journal of Inorganic Biochemistry	1	4.16	3.94
Journal of the Institute of Brewing	1	1.76	1.69
Journal of Medical Internet Research	2	5.43	4.84
Journal of Neurochemistry	1	5.37	4.36
Journal of Neuroscience Research	1	4.16	3.22
Journal of Nutrition	1	4.80	3.72

Journal	Qty	I.F. 2020	I.S. 2020
Journal of Nutritional Biochemistry	1	6.05	5.73
Journal of Psychopharmacology	1	4.15	3.68
Journal of Psychosomatic Research	1	3.01	2.41
Journal of Stroke	1	/	4.60
Journal of Studies on Alcohol and Drugs	1	2.58	1.90
Journal of Substance Use	2	1.00	0.99
Journal of Thoracic and Cardiovascular Surgery	1	5.21	1.25
Journal of Wine Research	1	/	1.60
Journal of Youth and Adolescence	1	4.38	3.75
JMIR Research Protocols	1	/	1.25
Mediators of Inflammation	1	4.71	4.06
Metabolism: Clinical and Experimental	1	8.69	7.29
Metabolites	1	/	4.75
Molecular Genetics and Genomics	1	3.29	3.09
Molecular Medicine	1	6.35	5.58
Molecular Nutrition and Food Research	2	5.91	5.38
Molecular Psychiatry	1	16.00	10.23
Molecules	2	4.41	4.15
Nature Communications	1	14.92	13.78
Neural Plasticity	1	3.60	3.27
Neurochemical Research	1	4.00	3.59
Neurochemistry International	1	3.92	3.75
Neuromethods	1	/	0.46
Neuropharmacology	2	5.25	4.79
Neuropsychopharmacology	1	7.85	5.66
Neuroscience	1	/	17.15
Neuroscience and Biobehavioral Reviews	1	9.00	7.9
Neurotoxicology and Teratology	1	3.76	3.47
NFS Journal	1	/	3.11
Nordic Studies on Alcohol and Drugs	1	1.60	1.16
Nutrients	5	5.72	5.43
Nutrition and Cancer	1	/	2.61
Nutrition, Metabolism and Cardiovascular Diseases	3	4.22	3.58
Oncotarget	1	/	3.33

Journal	Qty	I.F. 2020	I.S. 2020
Oral Oncology	2	5.34	3.79
Oxidative Medicine and Cellular Longevity	1	6.54	5.60
Physiological Reviews	1	37.31	34.32
PLoS ONE	5	3.24	3.04
Porto Biomedical Journal	1	/	/
Preventive Medicine	1	4.02	3.45
Psychiatry Research	1	3.22	2.96
Psychiatric Genetics	2	2.46	1.77
Psychological Medicine	1	7.72	5.60
Psychological Science	1	7.03	5.32
Psychologie en Gezondheid	1	/	/
Psychology and Health	2	3.07	2.51
Psychology, Health and Medicine	1	2.42	1.97
Psychology of Violence	1	4.15	3.00
Psychopharmacology	7	4.53	3.97
Psychosomatic Medicine	1	/	3.09
Scandinavian Journal of Public Health	1	3.02	2.36
Stem Cells Translational Medicine	1	6.94	5.61
Substance Use and Misuse	2	2.16	1.90
Supportive Care in Cancer	1	3.60	2.97
Cochrane Database of Systematic Reviews	1	9.27	3.22
The Lancet	1	79.32	9.45
Toxicology Letters	1	4.37	3.93
Translational Psychiatry	1	6.22	5.69
Urology	1	2.65	1.55
World Journal of Gastroenterology	1	5.74	5.22
TOTAL	**317**		

The impact factor (IF), also denoted as Journal impact factor (JIF), of an academic journal is a measure of the yearly average number of citations to recent articles published in that journal. It is based on Web of Science data.

The impact score (IS), also denoted as Journal impact score (JIS), of an academic journal is a measure of the yearly average number of citations to recent articles published in that journal. It is based on Scopus data.

This list was compiled using the Resurchify website in 2021

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