***DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO***

**XXXIX Cycle**

**Project proposal for a PhD scholarship (with no financial support from Sapienza)**

**Title of the research: Role of one-carbon metabolism factors in NAFLD severity and possible implications in cognitive impairment.**

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https://www.ospedalebambinogesu.it/genetica-molecolare-dei-caratteri-complessi-103745/

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**Summary**

Several studies have been conducted in recent years on non-alcoholic fatty liver disease(NAFLD) and its evolution into non-alcoholic steatohepatitis (NASH). Although both mouse models and cohorts of adult patients have been considered, very little is known about the development of the disease in children and adolescents. Despitethere are conflicting data, it is well established that the onset of non-alcoholic fatty liver (NAFLD) results from an accumulation of fatty acids (>5%) within hepatocytes, and this establishes a state of inflammation that exacerbates the disease, thus leading to its progression to liver fibrosis. However, NAFLD and its progression have been associated with several co-morbidities including: obesity, dyslipidemia, hypertension, type 2 diabetes, cardiovascular disease, and kidney dysfunction. Moreover, several lines of evidence also proposed that NAFLD could be independently associated with cognitive impairment in both adults and children, thus suggesting a liver-brain axis that could explain the nexus between liver and neuron impairment.

Little hints suggest that one-carbon metabolism factors, includingVitamin B12, Folate and homocysteine,could be crucial actors in the connection between NAFLD and anxiety disorders.

Therefore, the main objective of our study will be to investigate the possible correlation between Vitamin B12, Folate and homocysteine levels with NAFLD severity, and the onset of cognitive impairment, such as anxiety, by using:

* A cohort of pediatric patients with NAFLD
* In vitro models that mimic hepatocellular damage occurring in human NAFLD and possible effects on neuronal markers of cognitive impairment.

**References**

* Choi JM, Chung GE, Kang SJ, Kwak MS, Yang JI, Park B, Yim JY. Association Between Anxiety and Depression and Nonalcoholic Fatty Liver Disease. Front Med (Lausanne). 2021 Jan18;7:585618.
* Noon SL, D'Annibale DA, Schwimmer MH, Shiels J, Arin J, Durelle J, Newton KP, Goyal NP, Schwimmer JB. Incidence of Depression and Anxiety in a Cohort of Adolescents With Nonalcoholic Fatty Liver Disease. J PediatrGastroenterolNutr. 2021 Apr 1;72(4):579-583.
* Mazzone L, Postorino V, De Peppo L, Della Corte C, Lofino G, Vassena L, Fatta L, Armando M, Bedogni G, Vicari S, Nobili V. Paediatric non-alcoholicFattyliverdisease: impact on patients and mothers' quality of life. HepatMon. 2013 Mar 12;13(3):e7871.
* Lama A, Pirozzi C, Severi I, Morgese MG, Senzacqua M, Annunziata C, Comella F, Del Piano F, Schiavone S, Petrosino S, Mollica MP, Diano S, Trabace L, Calignano A, Giordano A, Mattace Raso G, Meli R. Palmitoylethanolamidedampensneuroinflammation and anxiety-likebehavior in obese mice. Brain Behav Immun. 2022 May;102:110-123. doi: 10.1016/j.bbi.2022.02.008.

**Pertinent Publications of the proponent (last 5 years)**

1: Panera N, Braghini MR, Crudele A, Smeriglio A, Bianchi M, Condorelli AG, Nobili R, Conti LA, De Stefanis C, Lioci G, Gurrado F, Comparcola D, Mosca A, Sartorelli MR, Scoppola V, Svegliati-Baroni G, Trombetta D, **Alisi A**. Combination Treatment with Hydroxytyrosol and Vitamin E Improves NAFLD-RelatedFibrosis. Nutrients. 2022 Sep 14;14(18):3791. doi: 10.3390/nu14183791.

2: Mosca A, Mantovani A, Crudele A, Panera N, Comparcola D, De Vito R, BianchiM, Byrne CD, Targher G, **Alisi A**. Higher Levels of Plasma Hyaluronic Acid andN-terminal Propeptide of Type III Procollagen Are Associated With Lower KidneyFunction in Children With Non-alcoholic Fatty Liver Disease. Front Pediatr. 2022Jun 6;10:917714.doi: 10.3389/fped.2022.917714.

3: Mosca A, Della Volpe L, **Alisi A**, Veraldi S, Francalanci P, Maggiore G. Non-Invasive Diagnostic Test for Advanced Fibrosis in Adolescents With Non-AlcoholicFatty Liver Disease. Front Pediatr. 2022 Apr 26;10:885576. doi:10.3389/fped.2022.885576.

4: Buzova D, Braghini MR, Bianco SD, Lo Re O, Raffaele M, Frohlich J, Kisheva A, Crudele A, Mosca A, Sartorelli MR, Balsano C, Cerveny J, Mazza T, **Alisi A**,Vinciguerra M. Profiling of cell-free DNA methylation and histone signatures inpediatric NAFLD: A pilot study. HepatolCommun. 2022 Dec;6(12):3311-3323. doi:10.1002/hep4.2082.

5: Pastore A, Panera N, Mosca A, Caccamo R, Camanni D, Crudele A, De Stefanis C,Alterio A, Di Giovamberardino G, De Vito R, Francalanci P, Battaglia S, Muda AO,De Peppo F, **Alisi A**. Changes in Total Homocysteine and Glutathione Levels AfterLaparoscopic Sleeve Gastrectomy in Children with Metabolic-Associated FattyLiver Disease. Obes Surg. 2022 Jan;32(1):82-89. doi: 10.1007/s11695-021-05701-6.

6: Eslam M, Alkhouri N, Vajro P, Baumann U, Weiss R, Socha P, Marcus C, Lee WS, Kelly D, Porta G, El-Guindi MA, **Alisi A**, Mann JP, Mouane N, Baur LA, Dhawan A,George J. Defining paediatric metabolic (dysfunction)-associated fatty liverdisease: an international expert consensus statement. Lancet GastroenterolHepatol. 2021 Oct;6(10):864-873. doi: 10.1016/S2468-1253(21)00183-7.

7: Manco M, Panera N, Crudele A, Braghini MR, Bianchi M, Comparcola D, De VitoR, Maggiore G, **Alisi A**. Angiopoietin-2 levels correlates with disease activityin children with nonalcoholic fatty liver disease. Pediatr Res. 2022Jun;91(7):1781-1786. doi: 10.1038/s41390-021-01666-5.

8: Panera N, Meroni M, Longo M, Crudele A, Valenti L, Bellacchio E, Miele L,D'Oria V, Paolini E, Maggioni M, Fracanzani AL, **Alisi A**, Dongiovanni P. The KLBrs17618244 gene variantisassociated with fibrosing MAFLD by promotinghepaticstellate cellactivation. EBioMedicine. 2021 Mar;65:103249. doi: 10.1016/j.ebiom.2021.103249.

9: Mosca A, Crudele A, Smeriglio A, Braghini MR, Panera N, Comparcola D, Alterio A, Sartorelli MR, Tozzi G, Raponi M, Trombetta D, **Alisi A**. Antioxidantactivityof Hydroxytyrosol and Vitamin E reducessystemicinflammation in children withpaediatric NAFLD. Dig Liver Dis. 2021 Sep;53(9):1154-1158. doi:10.1016/j.dld.2020.09.021.

10: Crudele A, Panera N, Braghini MR, Balsano C, **Alisi A**. The pharmacologicaltreatment of nonalcoholic fatty liver disease in children. Expert Rev ClinPharmacol. 2020 Nov;13(11):1219-1227. doi: 10.1080/17512433.2020.1829468.

11: Dongiovanni P, Crudele A, Panera N, Romito I, Meroni M, De Stefanis C, PalmaA, Comparcola D, Fracanzani AL, Miele L, Valenti L, Nobili V, **Alisi A**. β-Klothogene variation is associated with liver damage in children with NAFLD. JHepatol. 2020 Mar;72(3):411-419. doi: 10.1016/j.jhep.2019.10.011.

12: Mosca A, Comparcola D, Romito I, Mantovani A, Nobili V, Byrne CD, **Alisi A**,Targher G. Plasma N-terminal propeptide of type III procollagen accuratelypredicts liver fibrosis severity in children with non-alcoholic fatty liverdisease. Liver Int. 2019 Dec;39(12):2317-2329. doi: 10.1111/liv.14225.

13: de Oliveira FL, Panera N, De Stefanis C, Mosca A, D'Oria V, Crudele A, DeVito R, Nobili V, **Alisi A**. The Number of Liver Galectin-3 Positive Cells IsDually Correlated with NAFLD Severity in Children. Int J Mol Sci. 2019 Jul14;20(14):3460. doi: 10.3390/ijms20143460.

14: Nobili V, **Alisi A**, Valenti L, Miele L, Feldstein AE, Alkhouri N. NAFLD inchildren: new genes, new diagnostic modalities and new drugs. Nat RevGastroenterol Hepatol. 2019 Sep;16(9):517-530. doi: 10.1038/s41575-019-0169-z.

15: Nobili V, Mantovani A, Cianfarani S, **Alisi A**, Mosca A, Sartorelli MR,Maffeis C, Loomba R, Byrne CD, Targher G. Prevalence of prediabetes and diabetesin children and adolescents with biopsy-proven non-alcoholic fatty liverdisease. J Hepatol. 2019 Oct;71(4):802-810. doi: 10.1016/j.jhep.2019.06.023.

16: Panera N, Barbaro B, Della Corte C, Mosca A, Nobili V, **Alisi A**. A review ofthe pathogenic and therapeutic role of nutrition in pediatric nonalcoholic fattyliver disease. Nutr Res. 2018 Oct;58:1-16. doi: 10.1016/j.nutres.2018.05.002.

17: Nobili V, **Alisi A**, Mosca A, Della Corte C, Veraldi S, De Vito R, De StefanisC, D'Oria V, Jahnel J, Zohrer E, Scorletti E, Byrne CD. Hepatic farnesoid Xreceptor protein level and circulating fibroblast growth factor 19 concentrationin children with NAFLD. Liver Int. 2018 Feb;38(2):342-349. doi:10.1111/liv.13531.

18: Kazankov K, **Alisi A**, Møller HJ, De Vito R, Rittig S, Mahler B, Nobili V, Grønbæk H. Macrophage Markers Are Poorly Associated With Liver Histology inChildren With Nonalcoholic Fatty Liver Disease. J Pediatr Gastroenterol Nutr.2018 Nov;67(5):635-642. doi: 10.1097/MPG.0000000000002111.

19: **Alisi A**, Pampanini V, De Stefanis C, Panera N, Deodati A, Nobili V,Cianfarani S. Expression of insulin-like growth factor I and its receptor in theliver of children with biopsy-proven NAFLD. PLoS One. 2018 Jul31;13(7):e0201566. doi: 10.1371/journal.pone.0201566.

20: Nobili V, **Alisi A**, Mosca A, Crudele A, Zaffina S, Denaro M, Smeriglio A,Trombetta D. The Antioxidant Effects of Hydroxytyrosol and Vitamin E onPediatric Nonalcoholic Fatty Liver Disease, in a Clinical Trial: A NewTreatment? Antioxid Redox Signal. 2019 Jul 10;31(2):127-133. doi:10.1089/ars.2018.7704.

21: Mantovani A, Scorletti E, Mosca A, **Alisi A**, Byrne CD, Targher G.Complications, morbidity and mortality of nonalcoholic fatty liver disease.Metabolism. 2020 Oct;111S:154170. doi: 10.1016/j.metabol.2020.154170.

22: Pierantonelli I, Lioci G, Gurrado F, Giordano DM, Rychlicki C, Bocca C,Trozzi L, Novo E, Panera N, De Stefanis C, D'Oria V, Marzioni M, Maroni L,Parola M, **Alisi A**, Svegliati-Baroni G. HDL cholesterol protects from liverinjury in mice with intestinal specific LXRα activation. Liver Int. 2020Dec;40(12):3127-3139. doi: 10.1111/liv.14712.

23: **AssociazioneItaliana per lo Studio del Fegato (AISF),**SocietàItaliana diDiabetologia (SID) and SocietàItalianadell'Obesità (SIO); Members of theguidelines panel; Coordinator; AISF Members; SID Members; SIO Members;Metodologists. Non-alcoholic fatty liver disease in adults 2021: A clinicalpractice guideline of the Italian Association for the Study of the Liver (AISF),the Italian Society of Diabetology (SID) and the Italian Society of Obesity

(SIO). Dig Liver Dis. 2022 Feb;54(2):170-182. doi: 10.1016/j.dld.2021.04.029.

24: Manco M, Crudele A, Mosca A, Caccamo R, Braghini MR, De Vito R, Alterio A,Pizzolante F, De Peppo F, **Alisi A**. LncOb rs10487505 variant is associated withleptin levels in pediatric non-alcoholic fatty liver disease. Pediatr Res. 2022Dec;92(6):1737-1743. doi: 10.1038/s41390-022-02032-9.

25: Dzudzor B, Hammond H, Tachi K, **Alisi A**, Vento S, Gyasi RK, Aheto JMK. Serum 25-hydroxyvitamin D and hyaluronic acid levels as markers of fibrosis inpatients with chronic liver disease at the main tertiary referral hospital inGhana: A case-control study design. Health Sci Rep. 2023 Feb 11;6(2):e1101. doi:10.1002/hsr2.1101.