Alcohol consumption and smoking dose dependently and synergistically worsen local pancreas damage

Further Hungarian Pancreatic Study Group authors
Bálint Erőss1,2,3, Péter Jenő Hegyi1,3, Szilárd Váncsa1,2,3, Rita Nagy1,2,3, Katalin Mára1,2, Klementina Ocska2,3, Márk Félix Juhász1, Marcell Imrei2,3, Mária Földi1,5, Szabolcs Kiss4,5, Balázs Csaba Németh6, Tamás Takács6, László Czakó6, Szilárd Gódi7, Judit Bajor7, Patrícia Sarlós7, László Gajdán8, Mária Papp9, József Hamvas10, Mátra Varga11, Melanía Macarie12, Imola Török12, János Novák13, Artautas Mickevicius14, Elena Ramirez Maldonado15, Shamil Galeev16, Ville Sallinen17, Barnabás Bod18, Ali Tüzün Ince19, Tamás Nagy20, Nándor Faluhelyi21, Noémi Gede1, Stefania Bundue1,2,22,23, Tamás Hussein1, Mónika Lipp1, Anna Németh1,2, Orsolya Urbán1, Dorothy Tarján1, Simon Tóth1, Daniel Pécsi3, Péter Varjú3, Noémi Zádori3

1Division of Pancreatic Diseases, Heart and Vascular Center, Semmelweis University, Budapest, Hungary
2Centre for Translational Medicine, Semmelweis University, Budapest, Hungary
3Institute for Translational Medicine, Szentágóthai Research Centre, Medical School, University of Pécs, Pécs, Hungary
4Centre for Translational Medicine, Department of Medicine, University of Szeged, Szeged, Hungary
5Heim Pál National Pediatric Institute, Budapest, Hungary
6Department of Medicine, University of Szeged, Szeged, Hungary
7Division of Gastroenterology, First Department of Medicine, University of Pécs, Medical School, Pécs, Hungary
8Szent György University Teaching Hospital of Fejér County, Székesfehérvár, Hungary
9Division of Gastroenterology, Department of Internal Medicine, University of Debrecen, Debrecen, Hungary
10Peterfy Hospital, Budapest, Hungary
11Department of Gastroenterology, BMKK Dr. Rethy Pal Hospital
12County Emergency Clinical Hospital of Târgu Mureș - Gastroenterology Clinic and University of Medicine, Pharmacy, Sciences and Technology "George Emil Palade", Targu Mures, Romania
13Pády Kálmán Hospital of Békés County, Gyula, Hungary
14Vilnius University Hospital Santaros Clinics, Vilnius, Lithuania
15General Surgery, Consorci Sanitari del Garraf, Sant Pere de Ribes, Barcelona, Spain
16Saint Luke Clinical Hospital, St. Petersburg, Russia
17Department of Transplantation and Liver Surgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
18Dr. Bugyi István Hospital, Szentes, Hungary
19Hospital of Bezmialem Vakif University, School of Medicine, Istanbul, Turkey
20Department of Laboratory Medicine, Medical School, University of Pécs, Pécs, Hungary
21Department of Medical Imaging, Medical School, University of Pécs, Pécs, Hungary
22Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
23Fundeni Clinical Institute, Bucharest, Romania
### Supplementary Table 1. CENTRE DISTRIBUTION

| Institute                                                                 | City                  | Country      | Number of cases |
|---------------------------------------------------------------------------|-----------------------|--------------|-----------------|
| First Department of Medicine, University of Pécs                         | Pécs                  | Hungary      | 877             |
| Department of Medicine, University of Szeged                              | Szeged                | Hungary      | 423             |
| Szent György University Teaching Hospital of County Fejér                 | Székesfehérvár        | Hungary      | 395             |
| Department of Internal Medicine, University of Debrecen                   | Debrecen              | Hungary      | 169             |
| Bajcsy-Zsilinszky Hospital                                                | Budapest              | Hungary      | 152             |
| Dr. Réthy Pál Hospital of County Békés                                    | Békéscsaba            | Hungary      | 67              |
| County Emergency Clinical Hospital - Gastroenterology and University of Medicine, Pharmacy, Sciences and Technology | Tragu Mures           | Romania      | 57              |
| Pándy Kálman Hospital of County Békés                                     | Gyula                 | Hungary      | 31              |
| Vílnius University Hospital Santariskiu Klinikos                          | Vílnius               | Lithuania    | 31              |
| General Surgery, Consorci Sanitari del Garraf, Sant Pere de Ribes         | Barcelona             | Spain        | 28              |
| Saint Luke Clinical Hospital                                              | St. Petersburg        | Russia       | 28              |
| Helsinki University Central Hospital                                      | Helsinki              | Finland      | 25              |
| Dr. Bugyi István Hospital                                                 | Szentes               | Hungary      | 23              |
| Hospital of Bezmialem Vakif University, School of Medicine               | Istanbul              | Turkey       | 20              |
| Markusovszky University Teaching Hospital                                 | Szombathely           | Hungary      | 18              |
| Borsod-Abauj-Zemplén County Hospital and University Teaching Hospital     | Miskolc               | Hungary      | 14              |
| Bács-Kiskun County Hospital                                               | Kecskemét             | Hungary      | 11              |
| Centrum péče o zaživaci trákti, Vitkovická nemoenice a.s.                 | Ostrava               | Czech Republic | 11          |
| Clinical Hospital Center Rijeka                                            | Rijeka                | Croatia      | 11              |
| Csongrád County Health Center                                            | Makó                  | Hungary      | 10              |
| Gomel Regional Clinical Hospital                                          | Gomel                 | Belarus      | 8               |
| Bogomolets National Medical University                                   | Kiev                  | Ukraine      | 8               |
| Department of Surgery, University of Debrecen                             | Debrecen              | Hungary      | 7               |
| Gastroenterology, Hepatology and Nutrition Centre, Pauls Stradins Clinical University Hospital | Riga                  | Latvia       | 6               |
| Polyclinic of Hospitaller Brothers of Saint John of God                   | Budapest              | Hungary      | 4               |
| Second Department of Medicine, Semmelweis University                      | Budapest              | Hungary      | 2               |
| Keio University                                                           | Tokyo                 | Japan        | 2               |
| Central Military Emergency Hospital "Dr Carol Davila"                     | Bucharest             | Romania      | 1               |
| Heim Pál National Pediatric Institute                                     | Budapest              | Hungary      | 1               |
| Medical Centre, Hungarian Defence Forces                                  | Budapest              | Hungary      | 1               |
| **Total**                                                                 |                      |              | **2 441**       |
Supplementary Table 2. CHARACTERISTICS OF THE ANALYSED COHORT

| Variable                                                | Value (n=2441) |
|---------------------------------------------------------|---------------|
| Age in years, median (IQR)                              | 57 (44–69)    |
| Male, n (%)                                             | 1 395 (57.1%) |
| Etiology, n (%)                                         |               |
| Biliary                                                 | 972 (39.8%)   |
| Alcoholic                                               | 475 (19.5%)   |
| Alcoholic and hypertriglyceridaemia                     | 57 (2.3%)     |
| Hypertriglyceridaemia                                   | 77 (3.2%)     |
| Post-ERCP                                               | 68 (2.8%)     |
| Idiopathic                                              | 442 (18.1%)   |
| Combined                                                | 89 (3.6%)     |
| Other                                                   | 261 (10.7%)   |
| Revised Atlanta classification                          |               |
| Mild, n (%)                                             | 1 738 (71.2%) |
| Moderate, n (%)                                         | 579 (23.7%)   |
| Severe, n (%)                                           | 124 (5.1%)    |
| Mortality, n (%)                                        | 67 (2.7%)     |
| Length of stay in days, median (IQR)                    | 8 (6–12)      |
| Patients with local complication, n (%)                 | 654 (26.8%)   |
| Acute pancreatic fluid collection, n (%)                | 545 (22.4%)   |
| Pseudocyst, n (%)                                       | 191 (7.8%)    |
| Acute necrotic collection, n (%)                        | 218 (8.9%)    |
| Patients with systemic complication, n (%)              | 205 (8.4%)    |
| Respiratory failure, n (%)                              | 140 (5.7%)    |
| Heart failure, n (%)                                    | 52 (2.1%)     |
| Renal failure, n (%)                                    | 87 (3.6%)     |
| New-onset diabetes, n (%)                               | 77 (3.2%)     |

ERCP: endoscopic retrograde cholangiopancreatography
IQR: interquartile range
Supplementary Table 3. DATA QUALITY OF THE ANALYSED COHORT

| Synergistic effect                        | Total cohort | Uploaded data | %    |
|-------------------------------------------|--------------|---------------|------|
| Age                                       | 2,441        | 2,441         | 100.0% |
| Sex                                       | 2,441        | 2,441         | 100.0% |
| Etiology                                  | 2,441        | 2,441         | 100.0% |
| Severity (mild/moderate/severe)           | 2,441        | 2,441         | 100.0% |
| Mortality                                 | 2,441        | 2,441         | 100.0% |
| Local complications                       | 2,441        | 2,421         | 99.2%  |
| Fluid collection                          | 2,441        | 2,422         | 99.2%  |
| Pseudocyst                                | 2,441        | 2,422         | 99.2%  |
| Necrosis                                  | 2,441        | 2,421         | 99.2%  |
| Diabetes as complication                  | 2,441        | 2,441         | 100.0% |
| Systemic complications                    | 2,441        | 2,433         | 99.7%  |
| Respiratory failure                       | 2,441        | 2,432         | 99.6%  |
| Heart failure                             | 2,441        | 2,433         | 99.7%  |
| Renal failure                             | 2,441        | 2,433         | 99.7%  |
| Smoking status                            | 2,441        | 2,441         | 100.0% |
| Alcohol consumption status                | 2,441        | 2,410         | 98.7%  |
| Smoking amount                            | 2,441        | 2,407         | 98.6%  |
| Alcohol consumption amount                | 2,441        | 1,777         | 72.8%  |
| Amylase                                   | 2,441        | 2,266         | 92.8%  |
| Lipase                                    | 2,441        | 1,732         | 71.0%  |
| RAP                                       | 2,441        | 2,441         | 100.0% |
| CP                                        | 2,441        | 2,441         | 100.0% |
| **Overall**                               | **53,702**   | **51,978**    | **96.8%** |

**Smoking dose dependency**

| Smoking dose dependency                  | Total cohort | Uploaded data | %    |
|------------------------------------------|--------------|---------------|------|
| Local complications                      | 2,407        | 2,386         | 99.1% |
| Amylase                                  | 2,407        | 2,237         | 92.9% |
| Lipase                                   | 2,407        | 1,705         | 70.8% |
| RAP                                      | 2,407        | 2,407         | 100.0% |
| CP                                       | 2,407        | 2,407         | 100.0% |
| **Overall**                              | **12,035**   | **11,142**    | **92.6%** |

**Alcohol dose dependency**

| Alcohol dose dependency                  | Total cohort | Uploaded data | %    |
|------------------------------------------|--------------|---------------|------|
| Local complications                      | 1,777        | 1,762         | 99.2% |
| Amylase                                  | 1,777        | 1,649         | 92.8% |
| Lipase                                   | 1,777        | 1,231         | 69.3% |
| RAP                                      | 1,777        | 1,777         | 100.0% |
| CP                                       | 1,777        | 1,777         | 100.0% |
| **Overall**                              | **8,885**    | **8,196**     | **92.2%** |

RAP: recurrent acute pancreatitis, CP: chronic pancreatitis
## Supplementary Table 4. STATISTICAL RESULTS – DOSE DEPENDENCY

| SMOKING DOSE DEPENDENCY | NON-SMOKER | LIGHT SMOKER | HEAVY SMOKER | p*          |
|--------------------------|------------|--------------|--------------|-------------|
| AMYLASE (N=2237)         |            |              |              | <0.001      |
| N                        | 1,571      | 332          | 334          |             |
| Mean (SD)                | 1,206 (1,188) | 851 (952)    | 692 (788)    |             |
| Median (IQR)             | 831 (343, 1,681) | 496 (240, 1,112) | 398 (195, 808) |             |
| Minimum; Maximum         | 13; 8,544  | 30; 7,532    | 32; 4,852    |             |
| LIPASE (N=1705)          |            |              |              | <0.001      |
| N                        | 1,149      | 274          | 282          |             |
| Mean (SD)                | 2,916 (3,523) | 1,962 (2,398) | 1,587 (2,459) |             |
| Median (IQR)             | 1,675 (635, 3,846) | 1,027 (499, 2,508) | 822 (376, 1,692) |             |
| Minimum; Maximum         | 10; 24,940 | 14; 13,398   | 31; 20,569   |             |
| RAP AND CP (N=2407)      |            |              |              | <0.001      |
| RAP, n (%)               | 321 (19%)  | 94 (26%)     | 105 (29%)    | <0.001      |
| CP, n (%)                | 46 (2.7%)  | 41 (11%)     | 50 (14%)     | <0.001      |
| LOCAL COMPLICATIONS (N=2386) | 438 (26%) | 92 (26%)     | 109 (31%)    | 0.200       |

* Kruskal-Wallis rank sum test; Pearson's Chi-squared test

| ALCOHOL DOSE DEPENDENCY | NON-DRINKER | LIGHT DRINKER | HEAVY DRINKER | p*          |
|--------------------------|-------------|--------------|--------------|-------------|
| AMYLASE (N=1649)         |            |              |              | <0.001      |
| N                        | 1,158       | 186          | 305          |             |
| Mean (SD)                | 1,247 (1,216) | 821 (892)    | 663 (846)    |             |
| Median (IQR)             | 863 (366, 1,719) | 522 (230, 1,016) | 379 (180, 782) |             |
| Minimum; Maximum         | 13; 8,544   | 28; 5,283    | 30; 7,000    |             |
| LIPASE (N=1231)          |            |              |              | <0.001      |
| N                        | 845         | 153          | 233          |             |
| Mean (SD)                | 2,864 (3580) | 2,155 (2,575) | 1,723 (2,862) |             |
| Median (IQR)             | 1,571 (572, 3,756) | 1,276 (570, 2,681) | 736 (353, 1,730) |             |
| Minimum; Maximum         | 10; 24,940  | 110; 17,904  | 19; 20,569   |             |
| RAP AND CP (N=1777)      |            |              |              | <0.001      |
| RAP, n (%)               | 239 (19%)   | 50 (26%)     | 98 (30%)     | <0.001      |
| CP, n (%)                | 47 (3.7%)   | 16 (8.2%)    | 36 (11%)     | <0.001      |
| LOCAL COMPLICATIONS (N=1762) | 301 (24%) | 51 (26%)     | 109 (34%)    | 0.003       |

* Kruskal-Wallis rank sum test; Pearson's Chi-squared test

SD: standard deviation, IQR: interquartile range, RAP: recurrent acute pancreatitis, CP: chronic pancreatitis.
Supplementary Table 5. STATISTICAL RESULTS – SYNERGISTIC EFFECT

| SYNERGISTIC EFFECT | NS-ND | NS-D | S-ND | S-D | p* |
|---------------------|-------|------|------|-----|----|
| AGE (N=2441)        |       |      |      |     | <0.001 |
| Mean (SD)           | 1.049 | 639  | 202  | 551 |    |
| Median (IQR)        | 64 (50.76) | 59 (43.69) | 52 (42.60) | 47 (38.56) |    |
| Minimum/Maximum     | 18; 95 | 19; 95 | 18; 91 | 18; 82 |    |
| SEX (N=2441)        |       |      |      |     | <0.001 |
| Male, n (%)         | 356 (34%) | 470 (74%) | 102 (50%) | 467 (85%) |    |
| Female, n (%)       | 693 (66%) | 169 (26%) | 100 (50%) | 84 (15%) |    |
| SEVERITY (N=2441)   |       |      |      |     | 0.002 |
| Moderately severe, n (%) | 225 (21%) | 153 (24%) | 39 (19%) | 162 (29%) |    |
| Severe, n (%)       | 61 (5.8%) | 40 (6.3%) | 5 (2.5%) | 18 (3.3%) | 0.022 |
| Mortality, n (%)    | 32 (3.1%) | 23 (3.6%) | 2 (1.0%) | 10 (1.8%) | 0.100 |
| AMYLASE (N=2266)    |       |      |      |     | <0.001 |
| Mean (SD)           | 918 (381, 1.751) | 705 (298, 1.537) | 652 (309, 1.428) | 414 (197, 844) |    |
| LIPASE (N=1732)     |       |      |      |     | <0.001 |
| Mean (SD)           | 2.999 (3.684) | 2.788 (3.268) | 2.244 (3.024) | 1.637 (2.191) |    |
| RAP AND CP (N=2441) |       |      |      |     | <0.001 |
| RAP, n (%)          | 183 (17%) | 137 (21%) | 56 (28%) | 151 (27%) | <0.001 |
| CP, n (%)           | 28 (2.7%) | 18 (2.8%) | 19 (9.4%) | 76 (14%) | <0.001 |

NS–ND: non-smoking–non-drinking; NS–D: non-smoking–drinking; S–ND: smoking–non-drinking; S–D: smoking–drinking, SD: standard deviation, IQR: interquartile range, RAP: recurrent acute pancreatitis, CP: chronic pancreatitis.

* Kruskal-Wallis rank sum test; Pearson's Chi-squared test