

## Supplementary file 1

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**Alcohol consumption and smoking dose dependently and synergistically worsen local pancreas damage****Further Hungarian Pancreatic Study Group authors**

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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              |
| Pányi Kálmán Hospital of County Békés   | Gyula          | Hungary        | 31              |
| Vilnius University Hospital Santariskiu Klinikos  | Vilnius        | 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   | Szentendre     | Hungary        | 23              |
| Hospital of Bezmialem Vakif University, School of Medicine  | Istanbul       | Turkey         | 20              |
| Markusovszky University Teaching Hospital   | Szombathely    | Hungary        | 18              |
| Borsod-Abaúj-Zemplén County Hospital and University Teaching Hospital   | Miskolc        | Hungary        | 14              |
| Bács-Kiskun County Hospital   | Kecskemét      | Hungary        | 11              |
| Centrum péče o zažívaci trakt, Vítkovická nemocnice 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               |
| <b>Total</b>  |                |                | <b>2 441</b>    |

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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

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Supplementary Table 3. DATA QUALITY OF THE ANALYSED COHORT

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

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

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

RAP: recurrent acute pancreatitis, CP: chronic pancreatitis

## Supplementary file 1

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Supplementary Table 4. STATISTICAL RESULTS – DOSE DEPENDENCY

| SMOKING DOSE DEPENDENCY             | NON-SMOKER         | LIGHT SMOKER       | HEAVY SMOKER     | p*     |
|-------------------------------------|--------------------|--------------------|------------------|--------|
| <b>AMYLASE (N=2237)</b>             |                    |                    |                  |        |
| N                                   | 1 571              | 332                | 334              | <0.001 |
| 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        |        |
| <b>LIPASE (N=1705)</b>              |                    |                    |                  |        |
| N                                   | 1 149              | 274                | 282              | <0.001 |
| 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       |        |
| <b>RAP AND CP (N=2407)</b>          |                    |                    |                  |        |
| RAP, n (%)                          | 321 (19%)          | 94 (26%)           | 105 (29%)        | <0.001 |
| CP, n (%)                           | 46 (2.7%)          | 41 (11%)           | 50 (14%)         | <0.001 |
| <b>LOCAL COMPLICATIONS (N=2386)</b> |                    |                    |                  |        |
|                                     | 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*     |
|-------------------------------------|--------------------|--------------------|------------------|--------|
| <b>AMYLASE (N=1649)</b>             |                    |                    |                  |        |
| N                                   | 1 158              | 186                | 305              | <0.001 |
| 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        |        |
| <b>LIPASE (N=1231)</b>              |                    |                    |                  |        |
| N                                   | 845                | 153                | 233              | <0.001 |
| 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       |        |
| <b>RAP AND CP (N=1777)</b>          |                    |                    |                  |        |
| RAP, n (%)                          | 239 (19%)          | 50 (26%)           | 98 (30%)         | <0.001 |
| CP, n (%)                           | 47 (3.7%)          | 16 (8.2%)          | 36 (11%)         | <0.001 |
| <b>LOCAL COMPLICATIONS (N=1762)</b> |                    |                    |                  |        |
|                                     | 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.

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Supplementary Table 5. STATISTICAL RESULTS – SYNERGISTIC EFFECT

| SYNERGISTIC EFFECT         | NS-ND              | NS-D               | S-ND               | S-D              | p*     |
|----------------------------|--------------------|--------------------|--------------------|------------------|--------|
| <b>AGE (N=2441)</b>        |                    |                    |                    |                  |        |
| N                          | 1 049              | 639                | 202                | 551              | <0.001 |
| Mean (SD)                  | 62 (18)            | 57 (15)            | 51 (14)            | 47 (12)          |        |
| Median (IQR)               | 64 (50, 76)        | 59 (45, 69)        | 52 (42, 60)        | 47 (38, 56)      |        |
| Minimum; Maximum           | 18; 95             | 19; 95             | 18; 91             | 18; 82           |        |
| <b>SEX (N=2441)</b>        |                    |                    |                    |                  |        |
| Male, n (%)                | 356 (34%)          | 470 (74%)          | 102 (50%)          | 467 (85%)        | <0.001 |
| Female, n (%)              | 693 (66%)          | 169 (26%)          | 100 (50%)          | 84 (15%)         |        |
| <b>SEVERITY (N=2441)</b>   |                    |                    |                    |                  |        |
| Moderately severe, n (%)   | 225 (21%)          | 153 (24%)          | 39 (19%)           | 162 (29%)        | 0.002  |
| 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  |
| <b>AMYLASE (N=2266)</b>    |                    |                    |                    |                  |        |
| N                          | 967                | 601                | 188                | 510              | <0.001 |
| Mean (SD)                  | 1 285 (1 233)      | 1 079 (1 101)      | 1 056 (1 117)      | 692 (764)        |        |
| Median (IQR)               | 918 (381, 1 751)   | 705 (298, 1 537)   | 652 (309, 1 428)   | 414 (197, 844)   |        |
| Minimum; Maximum           | 13; 8 544          | 28; 7 750          | 33; 7 532          | 23; 4 852        |        |
| <b>LIPASE (N=1732)</b>     |                    |                    |                    |                  |        |
| N                          | 690                | 458                | 152                | 432              | <0.001 |
| Mean (SD)                  | 2 999 (3 684)      | 2 788 (3 268)      | 2 244 (3 024)      | 1 637 (2 191)    |        |
| Median (IQR)               | 1 690 (623, 3 964) | 1 624 (678, 3 537) | 1 213 (426, 2 524) | 914 (454, 1 924) |        |
| Minimum; Maximum           | 10; 24 940         | 19; 18 380         | 14; 17 450         | 22; 20 569       |        |
| <b>RAP AND CP (N=2441)</b> |                    |                    |                    |                  |        |
| 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%)         |        |

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

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.