

Supplementary Table 1. Exclusion criteria

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| • Known or suspected hypersensitivity to trial products or related products. |
| • Treatment with any medication for diabetes other than metformin during the 90 days prior to screening (except for insulin treatment for acute illnesses for ≤ 7 days). |
| • Left handedness. |
| • Possessed < 6 years education. |
| • Incapability of completing brain MRI scanning. |
| • Nasal disease affecting olfactory function. |
| • Hepatic impairment with liver transaminases > 2 times upper normal limits. |
| • Renal impairment with an estimated glomerular filtration rate $< 45\text{ml/min/1.73m}^2$. |
| • Cardiac diseases (a history of unstable angina or myocardial infarction during the 90 days prior to screening or New York Heart Association class III or IV). |
| • History or presence of neurological or psychiatric disorders, pancreatitis, medullary thyroid carcinoma, multiple endocrine neoplasia type 2, repeated urinary infection, severe gastrointestinal diseases, intestinal surgery, and malignant neoplasms. |
| • Proliferative retinopathy or maculopathy requiring acute treatment (as verified by fundoscopy / fundus photography), performed within 90 days prior to randomization. |
| • Alcohol or drug misuse. |
| • Females who were pregnant, breast-feeding or intending to become pregnant, or of childbearing potential and not using adequate contraceptive |

methods throughout the trial.

Supplementary Table 2. Descriptive statistics and correlations for study variables

| Variables | M | SD | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|-------------------------------------|--------|--------|----------|---------|--------|--------|---------|---------|---------|---------|--------|-------|
| 1.Liraglutide treatment | 0.330 | 0.478 | 1.000 | | | | | | | | | |
| 2.Dapagliflozin treatment | 0.330 | 0.478 | -0.500** | 1.000 | | | | | | | | |
| 3.Acarbose treatment | 0.330 | 0.478 | -0.500** | -.500** | 1.000 | | | | | | | |
| 4.Waist circumference | -2.083 | 3.549 | -0.025 | -0.160 | 0.185 | 1.000 | | | | | | |
| 5.Body fat ratio | -1.870 | 1.591 | -0.077 | -0.040 | 0.117 | -0.047 | 1.000 | | | | | |
| 6.Fasting insulin | 2.082 | 8.138 | 0.060 | 0.043 | -0.103 | 0.005 | 0.043 | 1.000 | | | | |
| 7.Left hippocampal activation value | 0.289 | 0.579 | 0.339* | -0.067 | -0.272 | -.408* | -0.081 | -0.002 | 1.000 | | | |
| 8.Attention | 8.389 | 12.933 | 0.177 | 0.042 | -0.218 | 0.208 | -.449** | 0.061 | 0.205 | 1.000 | | |
| 9.Delayed memory | 3.417 | 5.749 | 0.524** | -0.165 | -.359* | 0.018 | -0.087 | -0.162 | 0.477** | 0.474** | 1.000 | |
| 10.Executive function (time) | -5.046 | 13.275 | -0.144 | -0.028 | 0.172 | -0.084 | 0.004 | -0.392* | 0.139 | -0.091 | -0.103 | 1.000 |

$N = 36$. Liraglutide treatment was coded as 0 = not allocated to liraglutide group, and 1 = allocated to liraglutide group. Dapagliflozin treatment was coded as 0 = not allocated to dapagliflozin group, and 1 = allocated to dapagliflozin group. Acarbose treatment was coded as 0 = not allocated to acarbose group, and 1 = allocated to acarbose group.

* $P < 0.05$, and ** $P < 0.01$ were considered significant.

Supplementary Table 3. Structural equation model results (direct effects)

| Path | Standardized path coefficient | Unstandardized path coefficient | SE | <i>P</i> value |
|---|-------------------------------|---------------------------------|-------|----------------|
| Liraglutide treatment → Left hippocampal activation value | 0.399 | 0.330 | 0.174 | 0.022 |
| Liraglutide treatment → Delayed memory | 11.067 | 0.410 | 3.842 | 0.004 |
| Waist circumference → Left hippocampal activation value | -0.065 | -0.401 | 0.024 | 0.006 |
| Left hippocampal activation value → Delayed memory | 7.540 | 0.337 | 3.171 | 0.017 |
| Body fat ratio → Attention | -1.583 | -0.440 | 0.540 | 0.003 |
| Liraglutide treatment → Attention | 1.720 | 0.144 | 1.798 | 0.339 |
| Fasting insulin → Executive function (time) | -0.628 | -0.386 | 0.252 | 0.013 |
| Liraglutide treatment → Executive function (time) | -3.346 | -0.121 | 4.288 | 0.435 |

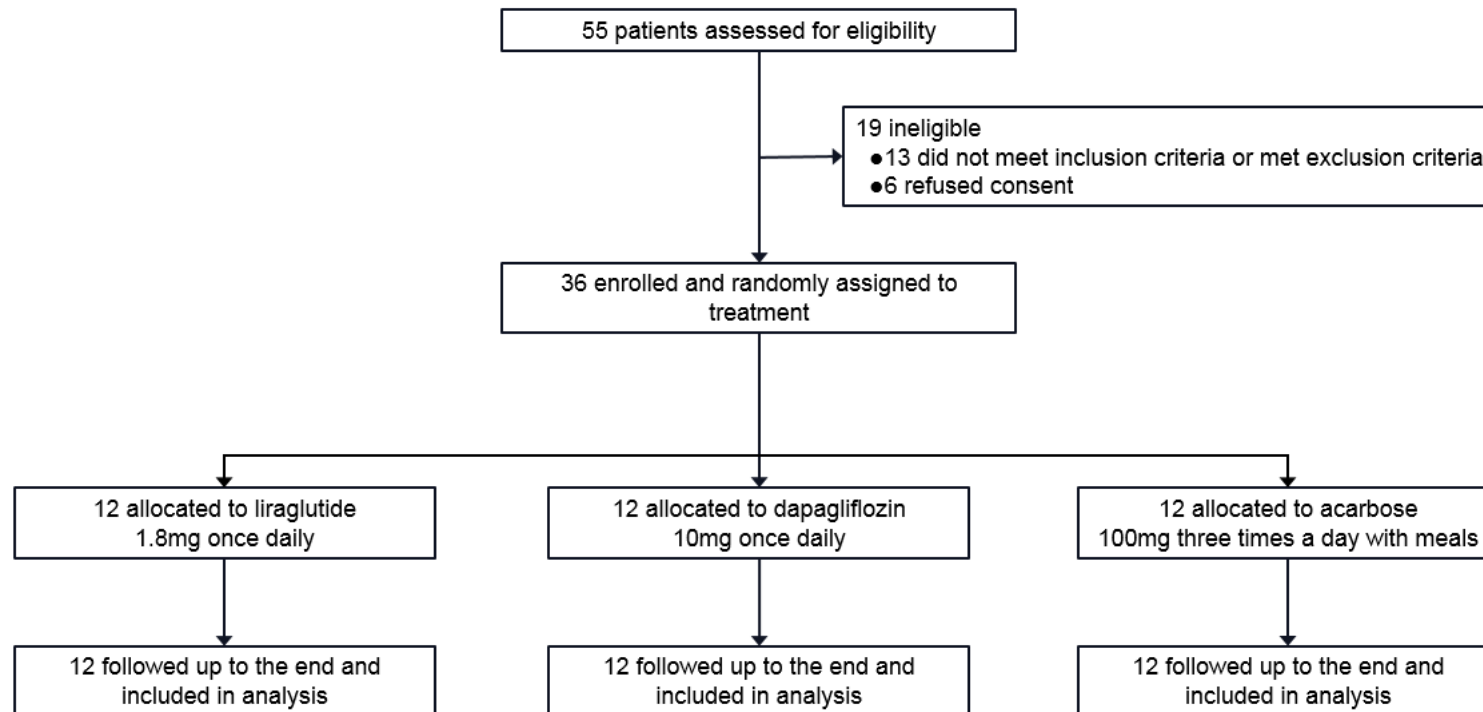
Liraglutide treatment was coded as 0 = not allocated to liraglutide group, and 1 = allocated to liraglutide group.

Supplementary Table 4. Bootstrap mediation test results

| Path | Standardized path coefficient | SE | Bias-corrected 95%CI | | | Mediating effect size (%) |
|---|-------------------------------------|-------|----------------------|-------|----------------|---------------------------------|
| | | | Lower | Upper | <i>P</i> value | |
| Liraglutide treatment → Left hippocampal activation value → Delayed memory (indirect effects) | 0.111 | 0.057 | 0.023 | 0.255 | 0.012 | 21.31% |
| Liraglutide treatment → Delayed memory (direct effects) | 0.410 | 0.128 | 0.142 | 0.638 | 0.003 | - |

Liraglutide treatment was coded as 0 = not allocated to liraglutide group, and 1 = allocated to liraglutide group.

Supplementary Figure 1. Trail profile of the study.



Supplementary Figure 2. Hypothesis structural equation model to assess the contributing factors attributed to the olfactory brain functional alterations and cognitive improvements. Metabolic parameters include the parameters either changed significantly after treatment in this study or showed significant association with cognition in our previous studies.

