### Supplementary Table 1. Clinical characteristics of the enrolled subjects

| Clinical characteristics | Control (n = 210) | CAD (n = 180) | P value |
|-------------------------|------------------|--------------|---------|
| Age (years)             | 58.5 (52.50-69.25) | 62 (55.00-67.00) | 0.4834 |
| Sex, male (%)           | 129 (61.40%)     | 117 (65.00%)  | 0.4660 |
| Diabetes, yes (%)       | 17 (8.10%)        | 39 (21.67%)   | <0.0001|
| Hypertension, yes (%)   | 53 (25.24%)       | 116 (64.44%)  | <0.0001|
| FPG (mmol/L)            | 5.36(5.04-5.77) | 5.75(5.14-6.83) | <0.0001|
| TC (mmol/L)             | 4.51(4.04-4.85)  | 4.15(3.51-4.92) | 0.0198 |
| TG (mmol/L)             | 1.08(0.87-1.33)  | 1.38(0.98-1.87) | <0.0001|
| LDL-C (mmol/L)          | 2.66(2.26-3.04)  | 2.47(1.91-3.16) | 0.2029 |
| HDL-C (mmol/L)          | 1.37(1.21-1.58)  | 1.12(0.88-1.38) | <0.0001|
| Hcy (μmol/L)            | 9.20 (2.93-10.95) | 11.52 (3.26-11.52) | <0.0001|
| Leukocytes (×10⁹)       | 5.64(4.80-6.41)  | 5.95(4.96-7.04) | 0.0383 |
| Neutrophil (×10⁹)       | 3.05(2.55-3.60)  | 3.72(2.98-4.69) | <0.0001|
| Monocyte (×10⁹)         | 0.39(0.32-0.47)  | 0.48(0.38-0.63) | <0.0001|
| Lymphocyte (×10⁹)       | 1.92(1.62-2.32)  | 1.50(1.16-1.83) | <0.0001|

Data are presented as median (interquartile range) or n (%).

Abbreviations: FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Hcy, homocysteine.

Significant P values were in bold.
### Supplementary Table 2. Clinical characteristics of the randomly selected subjects

| Clinical characteristics | Control (n = 112) | CAD (n = 110) | P value |
|--------------------------|------------------|--------------|---------|
| Age (years)              | 60 (53.25-70.00) | 61 (55.00-67.00) | 0.8515  |
| Sex, male (%)            | 70 (48.95%)      | 73 (51.05%)   | 0.5477  |
| Diabetes, yes (%)        | 5 (4.46%)        | 22 (20.00%)   | **0.0004** |
| Hypertension, yes (%)    | 33 (32.35%)      | 69 (67.65%)   | <**0.0001** |
| FPG (mmol/L)             | 5.43(5.13-5.76)  | 5.75(5.15-6.74) | **0.0008** |
| TC (mmol/L)              | 4.49(4.02-4.84)  | 4.16(3.45-4.94) | 0.1588  |
| TG (mmol/L)              | 1.12(0.86-1.36)  | 1.49(0.97-1.88) | <**0.0001** |
| LDL-C (mmol/L)           | 2.68(2.25-3.04)  | 2.48(1.89-3.15) | 0.4028  |
| HDL-C (mmol/L)           | 1.41(1.24-1.63)  | 1.12(0.88-1.37) | <**0.0001** |
| Hcy (μmol/L)             | 8.94(2.93-8.94)  | 11.52(3.26-11.52) | <**0.0001** |
| Leukocytes (×10⁹)        | 5.69(4.80-6.13)  | 5.80(4.94-6.75) | 0.7891  |
| Neutrophil (×10⁹)        | 2.99(2.51-3.67)  | 3.57(2.72-4.33) | **0.0018** |
| Monocyte (×10⁹)          | 0.40(0.33-0.48)  | 0.44(0.37-0.54) | **0.0041** |
| Lymphocyte (×10⁹)        | 1.96(1.66-2.33)  | 1.55(1.23-1.86) | <**0.0001** |

Data are presented as median (interquartile range) or n (%). Abbreviations: FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Hcy, homocysteine. Significant P values were in bold.
Supplementary Table 3. Independent risk factors for CAD

| Parameters          | Multivariate regressions |   |   |
|---------------------|--------------------------|---|---|
|                     | β(95%CI)                 | P |   |
| FPG                 | 1.56(1.11 - 2.21)        | 0.011 |   |
| LDL-C               | 0.55(0.32 - 0.94)        | 0.028 |   |
| TG                  | 3.63(1.53 - 8.63)        | 0.004 |   |
| HDL-C               | 0.31(0.10 - 0.92)        | 0.035 |   |
| Hcy                 | 1.14(1.05 - 1.24)        | 0.003 |   |
| cg25953130 Methy.   | 1.03(1.01 - 1.05)        | 0.012 |   |

Backward multivariate regression analysis was used to analyze the independent risk factors for CAD. Adjust for age, FPG, TC, TG, LDL-C, HDL-C, Hcy and leukocyte count.

Abbreviations: Methy., methylation; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Hcy, homocysteine; 95%CI, 95% confidence interval.

Significant P values were in bold.
## Supplementary Table 4. Bivariate and multivariate association between clinical parameters and the methylation levels of cg25953130

| Groups  | Parameters | Univariate correlations | Multivariate regressions |
|---------|------------|-------------------------|--------------------------|
|         |            | r    | P    | β (95%CI) | P    |
| Control | Age        | -0.2305 | 0.0145 | -0.24 (-0.59 - -0.10) | 0.0059 |
|         | FPG        | -0.1795 | 0.0606 | - | - |
|         | TC         | 0.0736 | 0.4404 | - | - |
|         | TG         | 0.2804 | **0.0027** | 0.21 (1.06 - 21.25) | **0.0307** |
|         | LDL-C      | 0.2984 | **0.0014** | - | - |
|         | HDL-C      | -0.1617 | 0.0884 | -0.03 (-13.70 - 9.50) | 0.7206 |
|         | Hcy        | 0.2589 | **0.0058** | 0.27 (0.45 - 2.04) | **0.0024** |
|         | Leukocytes | -0.1062 | 0.2649 | - | - |
| CAD     | Age        | 0.0986 | 0.3054 | 0.14 (-0.09 - 0.66) | 0.1375 |
|         | FPG        | -0.0504 | 0.6080 | - | - |
|         | TC         | -0.0781 | 0.4354 | - | - |
|         | TG         | 0.0869 | 0.3848 | -0.01 (-2.78 - 2.59) | 0.9435 |
|         | LDL-C      | -0.0775 | 0.4389 | - | - |
|         | HDL-C      | -0.2907 | **0.0030** | -0.33 (-23.82 - -6.33) | **0.0009** |
|         | Hcy        | -0.1118 | 0.2492 | -0.08 (-0.73 - 0.29) | 0.3867 |
|         | Leukocytes | -0.1000 | 0.2986 | - | - |

In order to control the influence of confounding factors on the linear regression model, in the multivariate regression analysis, we first use Stepwise's statistical method to eliminate the variables with collinearity and establish the optimal regression model, in which the age, TG, Hcy and HDL-C parameters are incorporate into the regression model.

Abbreviations: FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Hcy, homocysteine; 95%CI, 95% confidence interval.

Significant P values were in bold.
**Supplementary Table 5.** Serum lipids, Hcy and FPG levels of mouse

| groups  | TC (mmol/L) | TG (mmol/L) | LDL-C (mmol/L) | HDL-C (mmol/L) | FPG (mmol/L) | Hcy (μmol/L) |
|---------|-------------|-------------|----------------|----------------|--------------|--------------|
| G1      | 2.54±0.58   | 0.65±0.20   | 0.24±0.08      | 1.59±0.20      | 3.14±1.21    | 15.04±1.75   |
| G2      | 14.94±2.47  | 0.75±0.08   | 2.22±0.44      | 0.71±0.13      | 3.24±1.13    | 13.97±2.10   |
| G3      | 20.46±7.87  | 0.97±0.60   | 4.09±2.46      | 0.66±0.15      | 5.21±1.79    | 9.21±1.14    |
| G4      | 13.38±2.70  | 0.65±0.22   | 1.86±0.42      | 0.72±0.10      | 3.98±1.06    | 12.83±1.27   |
| G5      | 14.89±2.71  | 0.95±0.29   | 2.45 (2.19-2.50) | 0.82±0.16    | 2.78±0.53    | 28.77±7.85   |
| G6      | 11.16±1.91  | 0.66±0.13   | 1.95±0.17      | 0.55±0.11      | 2.57±0.73    | 19.52±3.95   |
| G7      | 15.98±3.49  | 0.77±0.15   | 2.54±0.67      | 0.75±0.15      | 3.82±0.84    | 30.90±8.14   |

Data are presented as mean ± SD (standard deviation) or as median (interquartile range).

Mice were divided into seven subgroups: G1, ApoE-WT + ND; G2, ApoE-/- + ND; G3, ApoE-/- + HFD; G4, ApoE-/- + HFD + FA; G5, ApoE-/- + ND + Hcy; G6, ApoE-/- + ND + Hcy + FA; G7, ApoE-/- + HFD + Hcy + FA.

Abbreviations: FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Hcy, homocysteine; WT, wild type; ND, normal diet; HFD, high fat diet; FA, folic acid.
| Species | Gene Name | Primers (5' to 3') |
|---------|-----------|--------------------|
| Human   | GAPDH     | Forward: GAAGGTGAAGGTCGGAGTC  
Reverse: GAAGATGGGTAGGGATTTG |
|         | DNMT1     | Forward: ACCGCTTCTCTTCTCAGGCACTTA  
Reverse: GTTCAGTCTCTGTGAACACTGTGG |
|         | ARID5B    | Forward: GAATTAGGCGGTAATCTGGGAG  
Reverse: TCCGAGGTTTGGATTGGAGCCAG |
|         | MCP-1     | Forward: AAGTGTCCTCAAAGAGCTGTC  
Reverse: AGTTTGGGTTTGCTTGTCAG |
|         | CCR2      | Forward: TACGGTGCTCCCTGTCAATAAA  
Reverse: TAAGATGAGGACGACCGAGCAT |
|         | CD86      | Forward: CTGCTCATCTATACACGGTTACC  
Reverse: GAAACGTCGTACAGTTCTGTG |
|         | IL-10     | Forward: GACTTTAAGGGTTACCTGGTTG  
Reverse: TCACATGCGCCTTGATGTCTG |
|         | Arg-1     | Forward: TGGACAGACTAGGAATTGGCA  
Reverse: CCAGTCCGTAACATCAAAAACT |
|         | TNF-α     | Forward: AGAAGCTCAGGGGCGCTACA  
Reverse: GCTCCGTGTCTCAAGGAAAGT |
| Mouse   | GAPDH     | Forward: AGGTCGGGTGTAACGGGATTG  
Reverse: TGTAGACCAGTGTAGGGGTCA |
|         | DNMT1     | Forward: AAGATGGGTGTGGTCTACCC  
Reverse: CATCCAGGTTGCTCCCTTG |
|         | ARID5B    | Forward: TTCCCTCCCAAGAGCACTCC  
Reverse: CTGCCGTTTCTCCCGAGAG |
|         | MCP-1     | Forward: TAAAAACCTGGAGACGAAACCT  
Reverse: GCATTAGCCTGAGGATGACG |
|         | TNF-α     | Forward: CCTCAACACTGATCTTCCTTCT  
Reverse: GCTACGACGTGGGTACGAG |
Supplementary Fig. 1. Spearman correlation analysis. (A, B) Spearman correlation between the methylation levels of cg25953130 and the expression of ARID5B in the CAD and control groups. (C) Spearman correlation between Hcy levels and the expression of CCR2 on classical monocytes in the control group. (D) Spearman correlation between HDL-C levels and the expression of CCR2 on classical monocytes in the CAD group. Abbreviations: m1, classical monocytes; Con, control.
Supplementary Fig. 2. The effects of Hcy, ox-LDL and FA on DNMT1 and ARID5B expression in primary monocytes. (A, B) The effect of folic acid on the expression of DNMT1 and ARID5B in Hcy-treated primary monocytes. (C, D) The effect of folic acid on the expression of DNMT1 and ARID5B in ox-LDL-treated primary monocytes. All plotted values are the mean ± SE values of at least 3 independent experiments.

Abbreviations: FA, folic acid; Hcy, homocysteine; ox-LDL, oxidized low density lipoprotein.

* P < 0.05, ** P < 0.01, **** P < 0.0001.
Supplementary Fig. 3. The effect of folic acid on the lipid and Hcy metabolism in mice. (A-D) The effect of folic acid on serum TC, LDL-C, HDL-C and TG in mice. (E) The effect of folic acid on serum Hcy in mice. (F) The effect of folic acid on serum FPG in mice. Mice were divided into seven subgroups: G1, ApoE-WT + ND; G2, ApoE-/- + ND; G3, ApoE-/- + HFD; G4, ApoE-/- + HFD + FA; G5, ApoE-/- + ND + Hcy; G6, ApoE-/- + ND + Hcy + FA; G7, ApoE-/- + HFD + Hcy + FA. Abbreviations: FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Hcy, homocysteine; WT, wild type; ND, normal diet; HFD, high fat diet; FA, folic acid.

#, the G1 group was statistically different from the other 6 groups; * P < 0.05, ** P < 0.01, *** P < 0.001, **** P < 0.0001.
Supplementary Fig. 4. Gating strategy for human monocyte subsets. Circulating leukocytes in FSC/SSC dot plot were presented in supplementary Fig. 4A. In CD86/SSC dot plot, CD86 positive monocytes were firstly gated (P2, B). Subsequently, in the CD14/CD16 dot plot (C), based on the expression of CD14 and CD16, the identified monocytes were divided into classical (P2, CD14++CD16-), intermediate (P3, CD14++CD16+) and nonclassical (P4, CD14+CD16++) subsets.
Supplementary Fig. 5. Gating strategy for mouse monocyte subsets. Circulating mouse leukocytes in FSC/SSC dot plot were presented in supplementary Fig. 5A. In SSC/CD115 dot plot, CD115 positive monocytes were firstly gated (P1, B). Subsequently, in the Ly6C/CD43 dot plot (C), based on the expression of Ly6C and CD43, the identified monocytes were divided into classical (P2, Ly6C++CD43+), intermediate (P3, Ly6C++CD43++) and nonclassical (P4, Ly6C+CD43++) subsets.
Supplementary Fig. 6. Gating strategy for monocyte subsets sorting and purity identification. Circulating monocytes in FSC/SSC dot plot were presented in supplementary Fig. 6A (P1). In CD86/SSC dot plot, CD86 positive monocytes were firstly gated (P2, B). Subsequently, in the CD14/CD16 dot plot, based on the expression of CD14 and CD16 (C), the identified monocytes were divided into classical (P3, CD14++CD16-), intermediate (P4, CD14++CD16+) and nonclassical (P5, CD14+CD16++) subsets. The monocyte subsets obtained by FCM sorting had good purity (D-F).
Supplementary Fig. 7. Purity identification for CD14+ monocytes. Flow cytometry was used to identify the purity of the obtained monocytes labeled with CD14 monoclonal fluorochrome-conjugated antibody. (A) Gating strategy for monocyte CD14+ monocytes. (B) Purity of the CD14+ monocytes.