Relation of Platelet Parameters With Incident Cardiovascular Disease (The Dongfeng-Tongji Cohort Study)

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Prospective studies on the relations between platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), and incident cardiovascular disease (CVD) were still limited. This study aimed to investigate the above-mentioned prospective relations in the middle-aged and older Chinese populations based on the Dongfeng-Tongji cohort. We included 31,751 participants who were free of coronary heart disease (CHD), stroke, cancer, or severely abnormal electrocardiogram at baseline. During a median follow-up of 5.9 years, we identified 5,683 incident CVD cases, including 4,423 CHD and 1,260 stroke cases. Cox proportional hazard models were used to estimate the hazard ratios (HRs) and 95% confident intervals (CIs) for the relation analyses. Compared with participants with 146 ≤ PLT ≤ 233 10E9/L, the adjusted HR (95% CI) of those with PLT < 146 10E9/L was 0.80 (0.68 to 0.95) for incident stroke. Compared with participants with 7.3 ≤ MPV ≤ 10.3 fl, the adjusted HRs (95% CIs) of those with MPV < 7.3 fl were 0.81 (0.75 to 0.88), 0.80 (0.73 to 0.88) and 0.84 (0.71 to 1.00) for incident CVD, CHD and stroke, respectively. Compared with participants with 13.2 ≤ PDW ≤ 18.1 %, the adjusted HRs (95% CIs) of those with PDW < 13.2 % were 0.80 (0.73 to 0.87) and 0.78 (0.70 to 0.86) for incident CVD and CHD, respectively. In conclusion, lower levels of PLT and MPV were significantly related to lower risk of stroke, while lower levels of MPV and PDW were significantly related to lower risks of CVD and CHD. **(Am J Cardiol 2019;123:239−248)**

Cardiovascular disease (CVD) has become the leading cause of morbidity and mortality worldwide, and coronary heart disease (CHD) and stroke are the major contributors to CVD.[1] Considering the increasing prevalence of CVD, useful markers for predicting future incident CVD are urgently needed. Platelets play a pivotal role in atherothrombosis,[2−4] which is the main pathological change and primary cause of CVD.[5] Platelet count (PLT), mean platelet volume (MPV) and platelet distribution width (PDW) are parameters reflecting the amount and size distribution of the peripheral platelets, which are low-costing and widely available in clinical blood routine. PLT, MPV, and PDW have been reported to be related to different cardiovascular events.[6−8] However, most studies focused on patient populations or regarded mortality as outcome rather than incident CVD. Therefore, this study aimed to investigate the prospective relations between PLT, MPV, PDW and incident CVD in a large cohort of Chinese general populations.

Methods

Data were collected from the DFTJ cohort in Shiyan, Hubei, China, and the details of the cohort have been described previously.[9] Briefly, 27,009 retired employees from the Dongfeng Motor Corporation (DMC) enrolled in this cohort in the baseline survey from September 2008 to June 2009. Then, we newly recruited 14,120 retired employees from DMC in the first follow-up survey from April to October 2013, and finally a total of 41,129 participants were included in this study. All participants completed baseline questionnaires, medical examinations and provided fasting blood samples. We excluded participants with CHD (n = 5,468), stroke (n = 1,972), cancer (n = 2,182), severely abnormal electrocardiogram (n = 674) at baseline or those who were loss to follow-up (n = 709), thus 31,751 eligible participants were included in this study. During a median follow-up of 5.9 years, we identified 5,683 incident CVD cases, including 4,423 CHD and 1,260 stroke cases, among 31,751 participants. Finally, we excluded those with missing or extreme data for three platelet parameters, leaving 26,492, 25,591 and 25,180 participants, respectively, for PLT, MPV and PDW analyses (Supplementary Figure S1).

Trained interviewers used a semistructured questionnaire to collect baseline information including sociodemographic characteristics, lifestyles, environmental exposures, family and medical histories. Physical examination was performed on all participants at DMC-owned

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hospital by trained physicians, nurses and technicians. Standing height, body weight, and waist circumference were measured in participants with light indoor clothing and without shoes. Body mass index was calculated as weight (kilogram) divided by height (meter) squared. Blood samples were collected after an overnight fast. PLT, MPV, PDW, serum lipids and fasting glucose (FG) were determined at the DMC-owned hospital's laboratory. The levels of PLT, MPV, and PDW were measured using a fully automated analyzer CELL-DYN 3700 (Abbott Laboratories. Abbott Park, Illinois). The levels of serum lipids and FG were measured with the ARCHITECT ci8200 automatic analyzer (Abbott Laboratories. Abbott Park, Illinois).

The diagnosis of CVD was made based on International Classification of Diseases (ICD) codes of the World Health Organization by cardiologists through medical insurance system and medical record reviews in the DMC-owned hospital. The outcome of the present study was incident CVD (ICD-10: I00-I99), including incident CHD (ICD-10: I20-I25 and I46) and stroke (ICD-10: I60, I61, I63, I64, I69.0, I69.1, I69.3, and I69.4).[10] We defined incident CHD as the first hospital admission with an occurrence of an angina pectoris, acute myocardial infarction, subsequent myocardial infarction, other forms of acute or chronic heart disease, percutaneous transluminal coronary angioplasty or coronary artery bypass graft, and cardiac arrest or death with CHD as the underlying cause.[11] Acute coronary syndrome (ACS) was a severe type of CHD, including acute myocardial infarction and unstable angina.[12] Stroke was defined as sudden or rapid onset of a typical neurological deficit of vascular origin that persisted more than 24 hours or till death.[13] Stroke subtypes were classified into ischemic stroke (IS) and hemorrhagic stroke (HS)[14] by physicians according to computed tomography and/or magnetic resonance imaging diagnoses.

Baseline characteristics were presented as a number (%) for categorical variables, mean ± SD for normally distributed variables and median (IQR) for non-normally distributed variables. Categorical variables were analyzed with Chi-square tests and continuous variables were analyzed with linear regression analyses. According to 20th and 80th percentiles of each platelet parameter, included participants were categorized into the following three groups: the lower group (20%), the middle group (60%), and the higher group (20%). We used Cox proportional hazard models to evaluate the relations between PLT, MPV, PDW and incident CVD, including CHD, stroke, and their subtypes. Model 1 stratified for age-at-risk[15] and adjusted for gender and admission batch. Model 2 additional adjusted for smoking status, alcohol drinking status, body mass index, history of diabetes mellitus (DM), history of hypertension, history of hyperlipidemia, history of platelet influential drug use (including anticoagulation drugs, aspirin and thrombolytic drugs), family history of CVD/CHD/stroke, physical activity (yes, no) and education. We further conducted stratified analyses by baseline characteristics such as age, gender, current smoker, low density lipoprotein (LDL) and FG levels to explore whether the relations between platelet parameters with incident CVD/CHD/stroke varied in different subgroups. Moreover, the potential interactions between main characteristics and PLT, MPV, PDW on incident CVD/CHD/stroke were tested by including the respective multiplicative interaction terms in the model 2. Finally, the restricted cubic splines with 4 knots were used to describe the relations between PLT, MPV, PDW and risk of CVD/CHD/stroke. Statistical analyses were performed using SAS 9.4 (SAS institute Inc., Cary, NC). Differences were considered significant if the two-tailed p value was less than 0.05.

Results

Baseline characteristics of study participants were displayed in Table 1. Participants who had higher PLT levels were more likely to be younger, females, more educated, current nonsmokers or nondrinkers, with higher white cell count or lower red cell volume, MPV and PDW levels, and more likely to have history of hyperlipidemia. Participants who had higher MPV levels were more likely to be younger, females, current nonsmokers, with higher white cell count or lower PLT levels. Participants who had higher PDW levels were more likely to have lower PLT levels or history of DM.

Table 2 presented the adjusted hazard ratios (HRs) (95% CIs) of cardiovascular events. Decreasing levels of PLT were significantly related to lower risk of stroke, and the adjusted HR (95% CI) of participants with PLT < 146 10E9/L was 0.77 (0.65 to 0.91; $P_{trend} = 0.010$) in model 1, compared with those with 146 ≤ PLT ≤ 233 10E9/L. However, the relations of PLT with stroke subtypes were inconsistent in model 1. Compared with participants with 146 ≤ PLT ≤ 233 10E9/L, the adjusted HR (95% CI) of those with PLT < 146 10E9/L was 0.71 (0.58 to 0.86; $P_{trend} < 0.001$) for incident IS while the adjusted HR (95% CI) of those with PLT > 233 10E9/L was 0.63 (0.40 to 0.98) for incident HS. Similar results were found in model 2, the relations between PLT and stroke/IS/HS were a little attenuated but still significant. Decreasing levels of MPV were significantly related to lower risks of CVD/CHD/ACS/stroke/IS in model 1. Compared with participants with 7.3 ≤ MPV ≤ 10.3 fl, the adjusted HRs (95% CIs) of those with MPV < 7.3 fl were 0.79 (0.73 to 0.86; $P_{trend} < 0.001$), 0.79 (0.72 to 0.86; $P_{trend} < 0.001$), 0.70 (0.60 to 0.81; $P_{trend} < 0.001$), 0.82 (0.69 to 0.97; $P_{trend} = 0.040$) and 0.77 (0.63 to 0.94; $P_{trend} = 0.032$) for incident CVD, CHD, ACS, stroke, and IS, respectively. Results obtained from model 2 were similar to model 1, though the protective effects of lower MPV levels for incident CVD/CHD/ACS/stroke/IS were a little weakened. Decreasing levels of PDW were significantly related to lower risks of CVD/CHD/ACS in model 1. Compared with participants with 13.2 ≤ PDW ≤ 18.1%, the adjusted HRs (95% CIs) of those with PDW < 13.2% were 0.80 (0.74 to 0.87; $P_{trend} < 0.001$), 0.78 (0.71 to 0.86; $P_{trend} < 0.001$) and 0.63 (0.53 to 0.74; $P_{trend} < 0.001$) for incident CVD, CHD and ACS respectively. The relations between PDW and CVD/CHD/ACS in model 2 were almost the same with those in model 1.

Table 1
Baseline characteristics of study participants

Variables	Platelet count (10E9/L)			p for trend*	Mean platelet volume (fl)			p for trend*	Platelet distribution width (%)			p for trend*
	<146	146-233	>233		<7.3	7.3-10.3	>10.3		<13.2	13.2-18.1	>18.1	
Participants	5194	16002	5296		4950	15737	4904		5046	14993	5141	
Age (years)	63.4 ± 8.1	61.6 ± 8.0	59.7 ± 8.1	<0.001	61.9 ± 7.9	61.8 ± 8.0	60.8 ± 8.3	<0.001	60.8 ± 8.0	61.9 ± 8.1	61.6 ± 8.2	<0.001
Female	2315 (44.6%)	8860 (55.4%)	3576 (67.5%)	<0.001	2689 (54.3%)	8814 (56.0%)	2917 (59.5%)	0.001	2859 (56.7%)	8479 (56.6%)	2857 (55.6%)	0.282
Primary school or below	1239 (24.0%)	3565 (22.4%)	1013 (19.3%)	<0.001	1107 (22.5%)	3614 (23.1%)	1126 (23.1%)	0.790	1093 (21.8%)	3511 (23.6%)	1138 (22.3%)	0.015
Waist circumference (cm)	82.1 ± 9.4	82.5 ± 9.2	82.7 ± 8.9	0.467	82.7 ± 9.2	82.5 ± 9.2	82.4 ± 9.2	0.567	83.7 ± 9.3	82.2 ± 9.2	81.9 ± 8.9	0.387
Body mass index (kg/m^2)	24.1 ± 3.4	24.2 ± 3.3	24.3 ± 3.3	0.592	24.3 ± 3.4	24.2 ± 3.3	24.1 ± 3.3	0.090	24.2 ± 3.4	24.2 ± 3.3	24.3 ± 3.2	0.004
Current smokers†	1061 (20.5%)	3109 (19.5%)	931 (17.6%)	0.022	982 (20.0%)	2999 (19.1%)	828 (17.0%)	0.008	1026 (20.5%)	2808 (18.8%)	907 (17.7%)	0.381
Current alcohol drinkers‡	1337 (25.8%)	4059 (25.4%)	1197 (22.6%)	<0.001	1276 (25.8%)	3803 (24.2%)	1158 (23.7%)	0.959	1285 (25.5%)	3564 (23.8%)	1279 (24.9%)	0.040
Physical activity§	3750 (72.2%)	11436 (71.5%)	3632 (68.6%)	0.001	3455 (69.8%)	11167 (71.0%)	3533 (72.0%)	0.373	3557 (70.5%)	10652 (71.0%)	3664 (71.3%)	0.931
Hyperlipidemia¶	1904 (36.7%)	6612 (41.3%)	2417 (45.6%)	<0.001	1983 (40.1%)	6713 (42.7%)	1906 (38.9%)	<0.001	2017 (40.0%)	6267 (41.8%)	2141 (41.6%)	0.454
Hypertension#	2505 (48.2%)	8120 (50.7%)	2764 (52.2%)	0.400	2527 (51.1%)	7961 (50.6%)	2466 (50.3%)	0.857	2562 (50.8%)	7519 (50.2%)	2657 (51.7%)	0.056
Diabetes mellitus**	922 (17.8%)	2624 (16.4%)	875 (16.5%)	0.439	737 (14.9%)	2703 (17.2%)	785 (16.0%)	0.006	706 (14.0%)	2445 (16.3%)	1021 (19.9%)	<0.001
Anti-platelet drug use	571 (11.0%)	1703 (10.6%)	554 (10.5%)	0.879	501 (10.1%)	1657 (10.5%)	514 (10.5%)	0.759	456 (9.0%)	1584 (10.6%)	574 (11.2%)	0.743
Red cell count (10E12/L)	4.6 ± 0.6	4.6 ± 0.5	4.5 ± 0.4	0.002	4.5 ± 0.5	4.6 ± 0.4	4.6 ± 0.5	0.883	4.5 ± 0.5	4.5 ± 0.4	4.6 ± 0.5	<0.001
Red cell volume (fl)	92.0 (89.3-94.8)	91.2 (88.7-94.0)	90.6 (87.8-94.0)	<0.001	92.1 (89.2-95.3)	91.2 (88.6-94.4)	91.1 (88.5-93.8)	0.316	93.2 (90.0-96.2)	91.0 (88.6-94.0)	91.0 (88.3-93.7)	0.004
White cell count (10E9/L)	5.2 (4.3-6.1)	5.6 (4.8-6.6)	6.2 (5.2-7.3)	<0.001	5.4 (4.6-6.5)	5.7 (4.8-6.8)	5.8 (4.9-6.9)	0.001	5.9 (4.9-7.0)	5.6 (4.7-6.7)	5.7 (4.8-6.8)	<0.001
Platelet count (10E9/L)	123.4 ± 17.4	187.3 ± 24.2	269.2 ± 30.2	<0.001	210.1 ± 57.3	197.9 ± 53.7	170.9 ± 47.1	<0.001	217.8 ± 59.1	195.2 ± 51.7	172.9 ± 51.2	<0.001
Mean platelet volume (fl)	9.5 (8.1-11.2)	8.7 (7.7-10.0)	8.2 (7.3-9.4)	<0.001	6.8 (6.4-7.1)	8.6 (7.9-9.4)	11.2 (10.7-11.9)	<0.001	9.4 (7.1-10.0)	8.2 (7.5-9.3)	9.6 (8.2-11.2)	<0.001
Platelet distribution width (%)	17.6 (16.3-18.9)	16.9 (14.7-17.9)	16.2 (12.6-17.2)	<0.001	16.3 (11.9 -17.2)	16.9 (14.7-17.8)	16.7 (14.0-18.9)	0.613	11.3 (9.8-12.2)	16.80 (15.9-17.4)	19.1 (18.5-20.0)	<0.001

Normally distributed variables were presented as mean ± SD, non-normally distributed variables were presented as median (IQR) and categorical variables were presented as a number (%).

* For linear trend, p values were derived from regression analyses for continuous variables and Chi-square tests for categorical variables.

† Current smokers were defined as participants who smoked at least one cigarette per day for more than half a year.

‡ Current alcohol drinkers were defined as participants who drank alcohol at least one time per week for more than half a year.

§ Physical activity was defined as exercise for more than 30 minutes every time and at least 5 times a week for more than half a year.

¶ Hyperlipidemia was defined as self-reported physician diagnosis of hyperlipidemia, or total cholesterol ≥ 6.22 mmol/L, or triglycerides ≥ 2.26 mmol/L, or high density lipoprotein < 1.04 mmol/L, or low density lipoprotein ≥ 4.14 mmol/L, or taking antihyperlipidemia medications.

Hypertension was defined as individuals with self-reported physician diagnosis of hypertension, or systolic blood pressure ≥ 140 mm Hg, or diastolic blood pressure ≥ 90 mm Hg, or use of antihypertensive medications.

** Diabetes mellitus was defined as self-reported physician diagnosis of diabetes, or fasting glucose ≥ 7.0 mmol/L, or taking antidiabetic medications (oral hypoglycemic medication or insulin).

Table 2
Adjusted hazard ratios of cardiovascular events according to groups defined by platelet parameters

	Platelet count (10E9/L)			p for trend*	Mean platelet volume (fl)			p for trend*	Platelet distribution width (%)			p for trend*
	< 146	146-233	>233		< 7.3	7.3-10.3	> 10.3		< 13.2	13.2-18.1	>18.1	
Cardiovascular disease												
Cases/Person-years	1058/30495	2973/91116	878/29128		812/30009	3108/94197	877/27168		727/27960	2965/90012	1055/30306	
model 1	0.96 (0.89-1.04)	1[Ref]	1.04 (0.96-1.12)	0.123	0.79 (0.73-0.86)	1[Ref]	1.01 (0.93-1.09)	<0.001	0.80 (0.74-0.87)	1[Ref]	1.05 (0.98-1.13)	<0.001
model 2	1.00 (0.93-1.08)	1[Ref]	1.00 (0.92-1.08)	0.845	0.81 (0.75-0.88)	1[Ref]	1.01 (0.93-1.09)	<0.001	0.80 (0.73-0.87)	1[Ref]	1.03 (0.96-1.11)	<0.001
Coronary heart disease												
Cases/Person-years	846/30984	2293/92767	692/29633		620/30577	2422/95874	696/27623		552/28474	2293/91678	847/30776	
Model 1	1.03 (0.95-1.12)	1[Ref]	1.04 (0.95-1.14)	0.820	0.79 (0.72-0.86)	1[Ref]	1.00 (0.91-1.09)	<0.001	0.78 (0.71-0.86)	1[Ref]	1.10 (1.01-1.20)	<0.001
Model 2	1.07 (0.99-1.17)	1[Ref]	1.00 (0.91-1.09)	0.208	0.80 (0.73-0.88)	1[Ref]	1.01 (0.92-1.10)	0.001	0.78 (0.70-0.86)	1[Ref]	1.08 (1.00-1.18)	<0.001
Acute coronary syndrome												
Cases/Person-years	331/28858	893/87166	253/27979		221/28895	960/89775	263/25957		171/27083	900/85767	362/28818	
Model 1	1.01 (0.88-1.15)	1[Ref]	1.01 (0.87-1.17)	0.994	0.70 (0.60-0.81)	1[Ref]	0.99 (0.86-1.15)	<0.001	0.63 (0.53-0.74)	1[Ref]	1.18 (1.03-1.34)	<0.001
Model 2	1.06 (0.93-1.21)	1[Ref]	0.97 (0.84-1.12)	0.304	0.72 (0.62-0.84)	1[Ref]	1.00 (0.87-1.16)	0.003	0.62 (0.53-0.74)	1[Ref]	1.16 (1.02-1.31)	<0.001
Stroke												
Cases/Person-years	212/32918	680/97524	186/31075		192/31698	686/101167	181/29045		175/29349	672/96658	208/32690	
model 1	0.77 (0.65-0.91)	1[Ref]	1.02 (0.86-1.21)	0.010	0.82 (0.69-0.97)	1[Ref]	1.04 (0.88-1.24)	0.040	0.91 (0.76-1.08)	1[Ref]	0.89 (0.76-1.05)	0.825
model 2	0.80 (0.68-0.95)	1[Ref]	0.97 (0.81-1.15)	0.109	0.84 (0.71-1.00)	1[Ref]	1.03 (0.87-1.22)	0.097	0.89 (0.74-1.06)	1[Ref]	0.88 (0.75-1.04)	0.692
Ischemic stroke												
Cases/Person-years	157/32762	536/96981	159/30980		146/31532	549/100670	145/28917		132/29197	539/96173	168/32556	
model 1	0.71 (0.58-0.86)	1[Ref]	1.12 (0.93-1.35)	<0.001	0.77 (0.63-0.94)	1[Ref]	1.03 (0.85-1.25)	0.032	0.85 (0.70-1.04)	1[Ref]	0.89 (0.74-1.06)	0.473
model 2	0.74 (0.61-0.90)	1[Ref]	1.07 (0.89-1.29)	0.004	0.79 (0.65-0.97)	1[Ref]	1.02 (0.84-1.23)	0.076	0.83 (0.68-1.02)	1[Ref]	0.87 (0.73-1.05)	0.396
Hemorrhagic stroke												
Cases/Person-years	55/32272	144/95627	27/30555		46/31111	137/99225	36/28514		43/28911	133/94693	40/32043	
model 1	0.99 (0.71-1.38)	1[Ref]	0.63 (0.40-0.98)	0.093	1.02 (0.71-1.47)	1[Ref]	1.10 (0.75-1.60)	0.734	1.14 (0.79-1.65)	1[Ref]	0.92 (0.63-1.33)	0.343
model 2	1.03 (0.74-1.45)	1[Ref]	0.60 (0.38-0.93)	0.038	1.05 (0.73-1.50)	1[Ref]	1.07 (0.74-1.57)	0.876	1.11 (0.77-1.60)	1[Ref]	0.91 (0.62-1.32)	0.410

Model 1: stratified for age-at-risk (in 5-year intervals) and adjusted for gender and admission batch.

Model 2: additionally adjusted for smoking status, alcohol drinking status, body mass index, history of diabetes mellitus, history of hypertension, history of hyperlipidemia, history of platelet influential drug use (including anticoagulation drugs, aspirin and thrombolytic drugs), family histories of cardiovascular disease/coronary heart disease/stroke, physical activity (yes/ no) and education.

* p value when we assigned the median value to each group and entered this as a continuous variable in the model to test its linear effect.

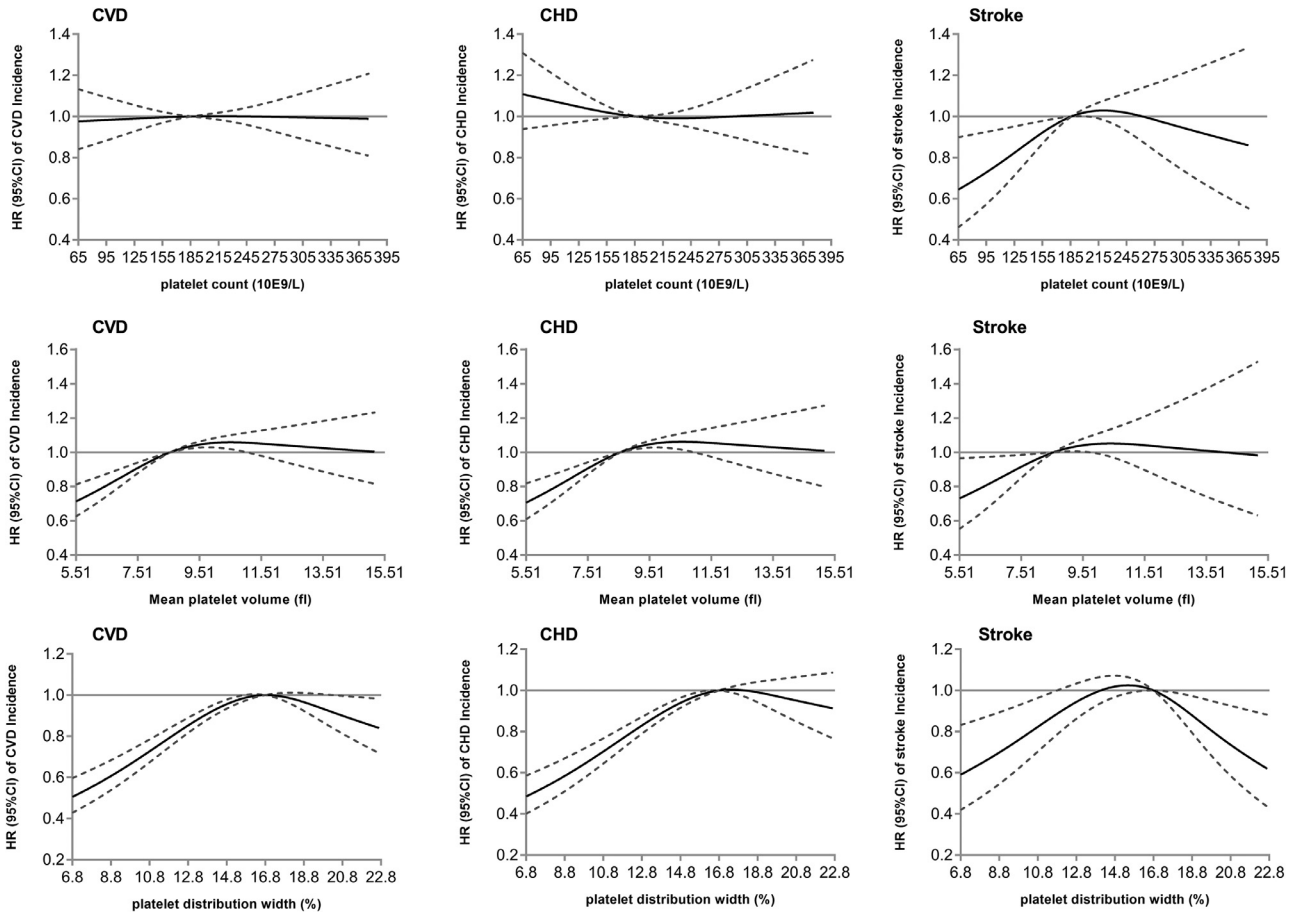

Figure 1. The restricted cubic splines for the associations between platelet parameters and incident cardiovascular events. Model 2 in Table 2 was used in this analysis. HR was calculated with natural value as a continuous variable, using the median value of each platelet parameter as reference. CHD, coronary heart disease; CI, confident interval; CVD, cardiovascular disease; HR, hazard ratio.

Restricted cubic spline plots showed that lower levels of PLT were related to the decreased risk of stroke, while lower levels of MPV and PDW were related to the decreased risks of CVD, CHD, and stroke respectively (Figure 1).

The increased risk of CHD with lower PLT levels was more obvious among participants who were ≥65 years old or with lower LDL levels, and significant interaction between PLT and LDL on risk of CHD was observed (p for interaction = 0.015). The decreased risk of stroke with lower PLT levels was more obvious among participants who were males, with lower LDL or FG levels (Table 3). The decreased risks of CVD/CHD/stroke with lower MPV levels were all more obvious among participants who were with lower LDL or higher FG levels (Table 4). The increased risks of CVD/CHD with higher PDW levels were all more obvious among participants who were <65 years old or with lower LDL levels, and significant interactions between PDW and age on risks of CVD/CHD were observed (all p for interaction < 0.05). The decreased risk of stroke with higher PDW levels was more obvious among participants who were with higher LDL or lower FG levels, and significant interaction between PDW and FG on risk of stroke was observed (p for interaction = 0.032, Table 5).

Discussion

To our knowledge, this study was first to investigate the prospective relations between PLT, MPV, PDW, and incident CVD, including CHD, stroke, and their subtypes in a large cohort of middle-aged and older Chinese populations. We found that lower levels of PLT and MPV were significantly related to lower risk of stroke, and lower levels of MPV and PDW were significantly related to lower risks of CVD and CHD.

In this prospective cohort study, we found that decreasing levels of PLT were related to lower risks of stroke and IS, while increasing levels of PLT were related to lower risk of HS. Different from this study, a cohort study[16] showed that higher risk of IS or HS was significantly related to higher or lower levels of PLT, respectively, with normal range (100 to 300 10E9/L) of PLT as the reference. Another study did not find any relation between PLT and stroke,[17] which could be due to their small sample size and less stroke cases. In addition, our results showed that decreasing levels of MPV were significantly related to lower risks of

Table 3
Adjusted hazard ratios of cardiovascular events for platelet count stratified by main characteristics

	Number[#]	Platelet count (10E9/L)			p for trend[*]	p for interaction[†]
		<146	146-233	>233		
Cardiovascular disease						
Age (years)						0.275
< 65	18224	0.99 (0.89-1.10)	1 [ref]	0.95 (0.86-1.05)	0.439	
≥ 65	8268	1.04 (0.95-1.15)	1 [ref]	1.01 (0.90-1.13)	0.610	
Gender						0.838
Male	11741	1.01 (0.91-1.11)	1 [ref]	1.00 (0.89-1.13)	0.950	
Female	14751	1.00 (0.89-1.12)	1 [ref]	0.99 (0.89-1.10)	0.915	
Current smoker						0.429
Yes	5101	0.91 (0.78-1.06)	1 [ref]	1.09 (0.93-1.28)	0.072	
No	21304	1.03 (0.95-1.12)	1 [ref]	0.97 (0.88-1.06)	0.242	
Low density lipoprotein levels (mmol/L)						0.205
< median (2.90)	13167	1.01 (0.91-1.12)	1 [ref]	1.07 (0.94-1.21)	0.441	
≥ median (2.90)	13281	1.03 (0.93-1.15)	1 [ref]	0.95 (0.85-1.05)	0.178	
Fasting glucose levels (mmol/L)						0.209
< median (5.60)	12737	0.92 (0.82-1.03)	1 [ref]	0.96 (0.85-1.09)	0.592	
≥ median (5.60)	13707	1.07 (0.97-1.18)	1 [ref]	1.02 (0.92-1.13)	0.448	
Coronary heart disease						
Age (years)						0.395
< 65	18224	1.05 (0.93-1.18)	1 [ref]	0.96 (0.86-1.07)	0.222	
≥ 65	8268	1.12 (1.00-1.24)	1 [ref]	0.99 (0.87-1.13)	0.104	
Gender						0.793
Male	11741	1.10 (0.98-1.23)	1 [ref]	0.99 (0.86-1.14)	0.139	
Female	14751	1.03 (0.91-1.17)	1 [ref]	1.01 (0.90-1.13)	0.824	
Current smoker						0.348
Yes	5101	0.99 (0.82-1.19)	1 [ref]	1.11 (0.92-1.33)	0.321	
No	21304	1.09 (0.99-1.20)	1 [ref]	0.96 (0.87-1.07)	0.055	
Low density lipoprotein levels (mmol/L)						0.015
< median (2.90)	13167	1.13 (1.00-1.27)	1 [ref]	1.13 (0.98-1.29)	0.884	
≥ median (2.90)	13281	1.05 (0.93-1.18)	1 [ref]	0.91 (0.81-1.03)	0.062	
Fasting glucose levels (mmol/L)						0.572
< median (5.60)	12737	1.03 (0.91-1.18)	1 [ref]	0.98 (0.86-1.12)	0.525	
≥ median (5.60)	13707	1.10 (0.99-1.23)	1 [ref]	1.01 (0.90-1.14)	0.273	
Stroke						
Age (years)						0.471
< 65	18224	0.81 (0.63-1.03)	1 [ref]	0.89 (0.71-1.12)	0.678	
≥ 65	8268	0.84 (0.68-1.03)	1 [ref]	1.04 (0.82-1.31)	0.108	
Gender						0.832
Male	11741	0.78 (0.64-0.96)	1 [ref]	1.02 (0.82-1.28)	0.041	
Female	14751	0.87 (0.65-1.17)	1 [ref]	0.90 (0.69-1.18)	0.985	
Current smoker						0.941
Yes	5101	0.76 (0.56-1.04)	1 [ref]	1.01 (0.75-1.36)	0.177	
No	21304	0.83 (0.68-1.01)	1 [ref]	0.97 (0.78-1.19)	0.256	
Low density lipoprotein levels (mmol/L)						0.085
< median (2.90)	13167	0.67 (0.53-0.86)	1 [ref]	0.87 (0.66-1.14)	0.091	
≥ median (2.90)	13281	0.98 (0.78-1.23)	1 [ref]	1.04 (0.83-1.29)	0.681	
Fasting glucose levels (mmol/L)						0.152
< median (5.60)	12737	0.59 (0.44-0.78)	1 [ref]	0.90 (0.69-1.17)	0.034	
≥ median (5.60)	13707	0.97 (0.79-1.20)	1 [ref]	1.00 (0.80-1.25)	0.854	

Model 2 in Table 2 was used in this analysis.

[#] Because of missing values for smoking status (n = 87), low density lipoprotein levels (n = 44) and fasting glucose levels (n = 48) hence not the same total number for each stratification characteristics.

[*] p value when we assigned the median value to each group and entered this as a continuous variable in the model to test its linear effect.

[†] p value were tested by including the respective multiplicative interaction terms between main characteristics and platelet count on incident cardiovascular disease/coronary heart disease/stroke.

CVD/CHD/stroke. A cohort study of 3,115 participants found that increased MPV was related to increased risk of CVD.[18] Two meta-analysis studies further identified that higher MPV was related to CHD, and suggested that MPV might be a useful prognostic biomarker for CVD.[19,20] There were also some disparate results. Giuseppe De Luca et al reported that MPV was not related to platelet aggregation and the extent of CHD,[21] and that MPV was also not related to platelet reactivity and the prevalence and extent of CHD in diabetic patients.[22] Furthermore, our results showed that decreasing levels of PDW were significantly related to lower risks of CVD/CHD. In an observational study of 679

Table 4
Adjusted hazard ratios of cardiovascular events for mean platelet volume stratified by main characteristics

	Number[#]	Mean platelet volume (fl)			p for trend[*]	p for interaction[†]
		<7.3	7.3-10.3	>10.3		
Cardiovascular disease						
Age (years)						0.305
< 65	17440	0.81 (0.73-0.91)	1 [ref]	0.97 (0.87-1.08)	0.029	
≥ 65	8151	0.87 (0.78-0.97)	1 [ref]	1.01 (0.91-1.12)	0.056	
Gender						0.894
Male	11171	0.81 (0.73-0.91)	1 [ref]	1.01 (0.90-1.12)	0.007	
Female	14420	0.80 (0.71-0.91)	1 [ref]	1.01 (0.91-1.13)	0.007	
Current smoker						0.616
Yes	4809	0.89 (0.76-1.05)	1 [ref]	1.02 (0.86-1.21)	0.231	
No	20664	0.79 (0.72-0.87)	1 [ref]	1.00 (0.92-1.10)	0.001	
Low density lipoprotein levels (mmol/L)						0.703
< median (2.90)	12709	0.69 (0.61-0.79)	1 [ref]	1.07 (0.96-1.20)	<0.001	
≥ median (2.90)	12810	0.94 (0.84-1.04)	1 [ref]	0.96 (0.86-1.07)	0.860	
Fasting glucose levels (mmol/L)						0.073
< median (5.60)	12337	0.91 (0.81-1.03)	1 [ref]	1.06 (0.95-1.20)	0.044	
≥ median (5.60)	13205	0.74 (0.67-0.83)	1 [ref]	0.97 (0.87-1.08)	0.001	
Coronary heart disease						
Age (years)						0.425
< 65	17440	0.84 (0.74-0.94)	1 [ref]	0.97 (0.86-1.09)	0.108	
≥ 65	8151	0.80 (0.70-0.91)	1 [ref]	1.03 (0.91-1.16)	0.005	
Gender						0.792
Male	11171	0.78 (0.68-0.89)	1 [ref]	1.01 (0.89-1.15)	0.005	
Female	14420	0.82 (0.72-0.94)	1 [ref]	1.01 (0.89-1.14)	0.033	
Current smoker						0.849
Yes	4809	0.81 (0.67-0.98)	1 [ref]	1.00 (0.82-1.22)	0.134	
No	20664	0.81 (0.72-0.89)	1 [ref]	1.01 (0.91-1.11)	0.003	
Low density lipoprotein levels (mmol/L)						0.874
< median (2.90)	12709	0.70 (0.60-0.80)	1 [ref]	1.05 (0.93-1.20)	<0.001	
≥ median (2.90)	12810	0.92 (0.81-1.03)	1 [ref]	0.97 (0.86-1.10)	0.576	
Fasting glucose levels (mmol/L)						0.094
< median (5.60)	12337	0.87 (0.76-1.00)	1 [ref]	1.07 (0.94-1.22)	0.025	
≥ median (5.60)	13205	0.76 (0.67-0.86)	1 [ref]	0.96 (0.85-1.08)	0.014	
Stroke						
Age (years)						0.544
< 65	17440	0.74 (0.58-0.95)	1 [ref]	0.98 (0.78-1.24)	0.115	
≥ 65	8151	1.09 (0.88-1.34)	1 [ref]	0.95 (0.75-1.20)	0.350	
Gender						0.869
Male	11171	0.91 (0.74-1.13)	1 [ref]	1.01 (0.81-1.26)	0.471	
Female	14420	0.73 (0.54-0.99)	1 [ref]	1.04 (0.80-1.36)	0.098	
Current smoker						0.225
Yes	4809	1.12 (0.83-1.50)	1 [ref]	1.08 (0.78-1.49)	0.900	
No	20664	0.74 (0.59-0.92)	1 [ref]	1.00 (0.82-1.23)	0.049	
Low density lipoprotein levels (mmol/L)						0.722
< median (2.90)	12709	0.68 (0.52-0.89)	1 [ref]	1.13 (0.89-1.44)	0.004	
≥ median (2.90)	12810	1.02 (0.81-1.27)	1 [ref]	0.95 (0.74-1.21)	0.630	
Fasting glucose levels (mmol/L)						0.646
< median (5.60)	12337	1.04 (0.81-1.35)	1 [ref]	1.03 (0.79-1.34)	0.947	
≥ median (5.60)	13205	0.69 (0.54-0.88)	1 [ref]	1.04 (0.83-1.30)	0.016	

Model 2 in Table 2 was used in this analysis.

[#] Because of missing values for smoking status (n = 118), low density lipoprotein levels (n = 72) and fasting glucose levels (n = 49) hence not the same total number for each stratification characteristics.

* p value when we assigned the median value to each group and entered this as a continuous variable in the model to test its linear effect.

[†] p values were tested by including the respective multiplicative interaction terms between main characteristics and mean platelet volume on incident cardiovascular disease/coronary heart disease/stroke.

patients with ACS from Turkey, researchers found that PDW was an independent predictor of in-hospital and long-term adverse cardiovascular events.[8] A cohort study, examined 3,115 participants enrolled in the Brazilian Longitudinal Study of Adult Health, found that increased PDW was also related to increased risk of CVD.[18] Other

Table 5
Adjusted hazard ratios of cardiovascular events for platelet distribution width stratified by main characteristics

	Number[#]	Platelet distribution width (%)			p for trend[*]	p for interaction[†]
		<13.2	13.2-18.1	>18.1		
Cardiovascular disease						
Age (years)						0.041
< 65	17195	0.84 (0.75-0.94)	1 [ref]	1.10 (1.00-1.21)	<0.001	
≥ 65	7985	0.75 (0.67-0.85)	1 [ref]	0.96 (0.87-1.06)	<0.001	
Gender						0.716
Male	10985	0.80 (0.71-0.90)	1 [ref]	1.04 (0.94-1.15)	<0.001	
Female	14195	0.79 (0.70-0.89)	1 [ref]	1.02 (0.92-1.14)	<0.001	
Current smoker						0.496
Yes	4741	0.77 (0.65-0.92)	1 [ref]	0.99 (0.84-1.16)	0.006	
No	20334	0.80 (0.73-0.88)	1 [ref]	1.05 (0.96-1.14)	<0.001	
Low density lipoprotein levels (mmol/L)						0.145
< median (2.90)	12495	0.77 (0.68-0.87)	1 [ref]	1.11 (1.00-1.24)	<0.001	
≥ median (2.90)	12609	0.85 (0.76-0.96)	1 [ref]	0.98 (0.88-1.08)	0.024	
Fasting glucose levels (mmol/L)						0.429
< median (5.60)	12076	0.77 (0.69-0.88)	1 [ref]	1.03 (0.91-1.17)	<0.001	
≥ median (5.60)	13048	0.82 (0.72-0.92)	1 [ref]	1.04 (0.95-1.14)	<0.001	
Coronary heart disease						
Age (years)						0.043
< 65	17195	0.84 (0.74-0.95)	1 [ref]	1.15 (1.03-1.28)	<0.001	
≥ 65	7985	0.71 (0.61-0.81)	1 [ref]	1.00 (0.89-1.12)	<0.001	
Gender						0.253
Male	10985	0.76 (0.66-0.87)	1 [ref]	1.14 (1.01-1.28)	<0.001	
Female	14195	0.79 (0.69-0.90)	1 [ref]	1.03 (0.91-1.16)	<0.001	
Current smoker						0.797
Yes	4741	0.76 (0.62-0.93)	1 [ref]	1.07 (0.89-1.29)	0.003	
No	20334	0.78 (0.70-0.87)	1 [ref]	1.08 (0.99-1.19)	<0.001	
Low density lipoprotein levels (mmol/L)						0.369
< median (2.90)	12495	0.75 (0.65-0.87)	1 [ref]	1.14 (1.01-1.29)	<0.001	
≥ median (2.90)	12609	0.83 (0.73-0.95)	1 [ref]	1.04 (0.93-1.17)	0.003	
Fasting glucose levels (mmol/L)						0.814
< median (5.60)	12076	0.75 (0.65-0.86)	1 [ref]	1.15 (1.01-1.31)	<0.001	
≥ median (5.60)	13048	0.81 (0.71-0.93)	1 [ref]	1.05 (0.94-1.16)	<0.001	
Stroke						
Age (years)						0.851
< 65	17195	0.87 (0.68-1.11)	1 [ref]	0.92 (0.73-1.15)	0.497	
≥ 65	7985	0.92 (0.73-1.17)	1 [ref]	0.87 (0.71-1.08)	0.922	
Gender						0.358
Male	10985	0.93 (0.75-1.16)	1 [ref]	0.81 (0.65-1.00)	0.573	
Female	14195	0.80 (0.60-1.08)	1 [ref]	1.01 (0.78-1.31)	0.159	
Current smoker						0.664
Yes	4741	0.82 (0.60-1.13)	1 [ref]	0.83 (0.61-1.14)	0.617	
No	20334	0.92 (0.74-1.13)	1 [ref]	0.90 (0.74-1.10)	0.875	
Low density lipoprotein levels (mmol/L)						0.182
< median (2.90)	12495	0.85 (0.65-1.10)	1 [ref]	1.03 (0.81-1.30)	0.180	
≥ median (2.90)	12609	0.97 (0.75-1.24)	1 [ref]	0.77 (0.61-0.98)	0.313	
Fasting glucose levels (mmol/L)						0.032
< median (5.60)	12076	0.92 (0.72 -1.19)	1 [ref]	0.65 (0.47-0.88)	0.361	
≥ median (5.60)	13048	0.84 (0.65 -1.09)	1 [ref]	1.02 (0.84-1.24)	0.178	

Model 2 in Table 2 was used in this analysis.

[#] Because of missing values for smoking status (n = 105), low density lipoprotein levels (n = 76), fasting glucose levels (n = 56) hence not the same total number for each stratification characteristics.

[*] p value when we assigned the median value to each group and entered this as a continuous variable in the model to test its linear effect.

[†] p values were tested by including the respective multiplicative interaction terms between main characteristics and platelet distribution width on incident cardiovascular disease/coronary heart disease/stroke.

conflicting data[23,24] showed that PDW might not be related to the extent of CHD, and could not be considered as a risk factor for CHD.

Until now, no prospective study had shown evidence that decreasing levels of MPV and PDW were related to lower risk of CVD in the Chinese general population. Several reasons could explain the disparity between our results and previous studies. In this study, the participants had a mean age of 61.7 years at baseline and they were followed for a median of 5.9 years. CHD and stroke were defined as CVD

outcomes, and a total of 5,683 CVD cases were documented from 31,751 subjects (17.9%). Therefore, the disparate results could also be due to inherent differences in population characteristics such as age distribution, different definitions of endpoints, and sample size.

The underlying mechanisms for decreased risk of CVD with lower levels of MPV and PDW were not fully understood, several plausible mechanisms could be involved. Firstly, large platelets, characterized by high MPV and PDW levels, were related to increased platelet activation which represented a major risk factor for atherothrombosis.[25,26] Secondly, large platelets that contained more dense granules were metabolically and enzymatically more active than small platelets and higher thrombotic potential.[27] Finally, activated platelets stimulated thrombus formation in response to rupture of an atherosclerotic plaque or endothelial cell erosion, promoting atherothrombotic disease.[28]

The main strengths of this study are the prospective design, the relatively large sample size, more incident cases, different cardiovascular outcomes, and the ability to adjust for a large number of potential confounders. There are also several limitations in the present study. Firstly, an important consideration was the variability in the timing and methods of blood sample preparation and the type and calibration of particle counters, which might have a vital impact on the measurement of PLT, MPV and PDW. Secondly, the study was carried out in middle-aged and older Chinese who were free of CHD, stroke, cancer, severely abnormal electrocardiogram, therefore our results may not be generalized to populations of all ages, different health conditions, or other ethnicities. Finally, although a wide range of potential confounding factors were included in our analysis, we could not rule out the possibility of residual and unmeasured confounders.

In conclusion, this study found that lower levels of PLT and MPV were significantly related to lower risk of stroke, while lower levels of MPV and PDW were significantly related to lower risks of CVD/CHD in the middle-aged and older Chinese populations. PLT, MPV, and PDW might be useful markers for the prediction of future incident CVD and for health management of middle-aged and older Chinese populations.

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Ethics approval and consent to participate

The protocol was approved by the Ethics Committee of Dongfeng General Hospital, DMC and the Medical Ethics Committee of the School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, and the study was subsequently carried out in accordance with the approved guidelines. All participants provided written informed consent.

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Disclosures

The investigators have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.10.016.

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