Review Article

Cardiovascular, diabetes, and cancer strips: evidences, mechanisms, and classifications

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Objectives: To report and name firstly that there are cardiovascular disease (CVD), diabetes mellitus (DM) and cancers (CDC) strips; and disclose their mechanisms, classifications, and clinical significances.

Study design: Narrative and systematic review study and interpretive analysis.

Methods: Data sources and study selection: to collect and present related evidences on CDC strips from evidence-based, open-access, both Chinese- and English-language literatures in recent 10 years on clinical trials from PubMed according to keywords "CVD, DM and cancers" as well as authors' extensive clinical experience with the treatment of more than fifty thousands of patients with CVD, diabetes and cancers over the past decades, and analyze their related mechanisms and categories which based on authors' previous works. Data extraction: data were mainly extracted from 48 articles which are listed in the reference section of this review. Qualitative, quantitative and mixed data were included, narratively and systematically reviewed.

Results: With several conceptual and technical breakthrough, authors present related evidences on CDC strips, these are, CVD and DM, DM and cancers, cancers and CVD linked, respectively; And "Bad SEED" +/– "bad soil" theory or doctrine may explain this phenomenon due to "internal environmental injure, abnormal or unbalance" in human body resulting from the role of risk factors (RFs) related multi-pathways and multi-targets, which including organ & tissue (e.g., vascular-specific), cell and gene-based mechanisms. Their classifications include main strips/type B, and Branches/type A as showed by tables and figures in this article.

Conclusions: There are CDC strips and related mechanisms and classifications. CDC strips may help us to understand, prevent, and control related common non-communicable diseases (NCDs) as well as these high risk strips.

Keywords: Cardiovascular disease (CVD); diabetes; cancer; evidence; mechanisms

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As we all known, chronic non-communicable diseases (NCDs) are now totally over 1.0 billion in the globe and may account for 85% of deaths nowadays. It's a big problem and challenge due to leading to 70% burden of public health. And we find that there is a common phenomenon of co-morbid diseases in NCD, especially three most commonly occurring, namely, cardiovascular diseases (CVDs), diabetes mellitus (DM), and cancers, which are responsible for more than 25 million deaths in the world each year, and millions more live with one or more of these diseases. They undermine health, shorten life expectancy, and cause enormous suffering, disability, and economic costs due to lifestyle changes, urbanization and longevity according to the USA agenda and the Report on Cardiovascular Diseases in China [2010] (1-4). Here, the authors found and firstly named it "CVD-DM-cancers

strips" (CDC strips) because they are linked with each other. NCD, especially CDC strips author discovered, are the major causes of morbidity and mortality, high direct cost of care, high indirect cost in loss of production. However, these strips could be prevented by controlling the modifiable risk factors (RFs).

In this article, with several conceptual and technical breakthroughs, we will present related evidences on CDC strips from open-access literatures on clinical trials as well as the great clinical experiences, and analyze its related categories and mechanisms which based on our previous works (5-9).

CDC strips: evidences

These evidences on CDC strips from open-access literatures are based on the linkages between CVD and DM, DM and cancers, cancers and CVD, respectively and each other. And we think these evidences are enough to support our views on CDC strips.

CVD and DM linked

CVD has a raised and potentially modifiable risk of type 2 diabetes (T2DM). Patients with coronary heart disease (CHD) and impaired fasting glucose (IFG) have a very high rate of conversion to T2DM (4).Those patients with more RFs, such as higher body-mass index (BMI), fasting glucose, C-reactive protein (CRP), triglycerides, homeostatic assessment of insulin resistance (HOMA-IR) and diastolic blood pressure at baseline, 44% developed diabetes. 26.7% overweight women with one or more cardio-metabolic high-risk factors developed gestational DM in a subsequent pregnancy (10). Thus, metabolic screening could be included in routine health assessments. In the Valsartan Antihypertensive Long-Term Use Evaluation trial, at baseline, more than 1/3 were diabetic, and during follow-up, new-onset diabetes was about 13% (3). There is a high prevalence and incidence of diabetes in patients with CHD and chronic heart failure (CHF) (11,12), and new onset diabetes is more likely to occur during treatment with ß-blockage.

Also, T2DM has a raised and potentially modifiable risk of CVD. Among screen-detected diabetes, 10-year risk of CHD was 11% in women and 21% in men. Among them, 73% had high blood pressure (HBP) and high cholesterol levels were in 70%. Definitely, T2DM was linked with CVD; especially those were not being treated. There were often micro-vascular or macro-vascular complications, peripheral vascular disease (PVD) in T2DM, but those patients who received intensive glucose therapy had a lower risk or a reduction in vascular events (13,14). Survival of coronary artery bypass grafting (CABG) surgery patients with diabetes is greatly affected by associated co-morbidities of PVD and renal failure (15). Suppression of atherosclerosis (AS) in T2DM with pioglitazone therapy is linked to its ability to raise HDL cholesterol for reducing carotid intima-media thickness (CIMT) progression (16). Besides, DM is highly associated with cardiomyopathy (17). Common RFs, such as BMI and waist circumference, were both strongly linked to CVD and especially to DM. The risk for T2DM was increased by 78% in the overweight group (18).

CVD is a major contributor to morbidity and mortality in T2DM. Patients with diabetes at baseline had the highest cardiac morbidity defined as myocardial infarction (MI) and HF with a hazard ratio of 2.20. Those with new-onset diabetes had significantly higher cardiac morbidity, especially more congestive HF (CHF), than those without diabetes, with a hazard ratio of 1.43 (3). The coincident linkage suggests that identification of the underlying genes may help clarify the relationship between diabetes, metabolic syndrome (MetS), and CVD (19). For example, there is often coronary artery calcification (CAC)—a marker of subclinical atherosclerosis in subjects with type 1 diabetes mellitus (T1DM) (20).

DM and cancers linked

DM has a raised and potentially modifiable risk of cancers. By examined the association of DM history with total and common site-specific cancers, scientists found that DM significantly increased the risk of liver cancer for both men and women. Significant increased and reduced risk due to DM for men were also found for non-Hodgkin lymphoma (NHL) and stomach cancer, respectively. For females, a reduced risk of stomach cancer due to DM was also revealed.

A history of T2DM is one of few consistent RFs for pancreatic cancer. Potentially modifiable RFs related to fasting insulin and glucose concentrations may influence its risk. Therefore, dietary fat associated with higher fasting insulin concentrations may increase its risk in smokers. Pancreatic cancer is a powerful diabetogenic state and appears to be associated with conventional RFs for DM. This DM is often new-onset; it is likely induced by the tumor.

Weight is associated with greater prostate cancer

mortality in men, which is mediated by mechanism(s) other than the characteristic metabolic alterations of diabetes. As the same, MetS was a RF for incident colorectal cancer in men but not women (21). It may be a marker encouraging tumor initiation, promotion, and/or progression.

DM is associated with breast cancer. Hyperinsulinemia and the MetS are both RFs for breast cancer. After the diagnosis, women with a BRCA1 or BRCA2 mutation face a 2-fold increase in the risk of diabetes (22). However, gestational DM was inversely associated with breast cancer in Hispanic women, a population with a high prevalence of diabetes and non-Hispanic Whites (23).

There was a significant positive correlation between acute lymphoblastic leukaemia (ALL) and T1DM, and the incidence of chemotherapy-induced transient hyperglycemia in childhood ALL is common.

DM and cancers incidence and mortality linked focused mainly upon T2DM. As incidence of T1DM increases, by around 3% annually among children, as well as the inconsistency within available results, it's necessary to study further its impact upon other cancers incidence and mortality increases.

Cancers and CVD linked

Cancers have a raised and potentially modifiable risk of CVD. CVD is the leading cause of late morbidity and death among cancer survivors. With the high rates of kidney cancer in European countries, there was an increased risk for self-reported hypertension (24). And polycystic ovary syndrome (PCOS) is also associated with increased risk of cardiovascular morbidity.

High-dose chemotherapy may develop late cardiotoxicity in cancer patients although it is very effective in children all (25). Angiotensin-converting enzyme inhibitors (ACEI), e.g., Enalapril or Perindopril seem to prevent elevations in troponin I or troponin T (26,27). Clinical and animal studies showed that increased TnI or TnT is an indicator of cardiotoxicity and poor cardiologic outcome (28,29). The LVEF significantly declined and a trend for LVEF to decline was observed in advanced non-small cell lung cancer (NSCLC) patients receiving cisplatin-gemcitabine (CG) or epirubicin-gemcitabine (EG) as first-line treatment resulting from cardiotoxicity due to irreversible cardiomyopathy (30). Onset of HBP during treatment for advanced NSCLC may be associated with improved outcomes. CVD or CVEs frequently occur after lymphoma therapy. Patients are at long-term high risk of CHF after doxorubicin-based chemotherapy for NHL and need therefore life-long monitoring (31), for example, genetic variation of human cytochrome p450 reductase as a potential biomarker (32). Gonadotropin-releasing hormone (GnRH) agonists are associated with greater risk of CHD and MI in men with prostate cancer (33), but it do not seem to increase cardiovascular mortality (CVM) in those. As literature reported, a history of chemotherapy-induced cardiomyopathy was present in 21%, and 5.7% had known AS disease. One fourth had hypertension; 32.1%, dyslipidemia and 13%, DM.

Atrial arrhythmias are common after thoracic surgery, and the incidence of no sustained ventricular tachycardia after major thoracic surgery is 15%. Postoperative cardiovascular events are often seen in patients with cancers. For example, postoperative supraventricular arrhythmias are a common complication in elderly patients undergoing lung resection surgery for lung cancer.

Among adult survivors, exposure to total body irradiation or abdominal plus chest radiation, and a sedentary life-style are associated with cardiovascular RF cluster (CVRFC). Radiation exposure (e.g., X-ray) during the diagnosis and treatment may lead to or increase risk of both CVD or CVEs and cancers. On the one hand, long-term survivors of cancers treated with radiation therapy have an increased incidence of irradiation-related CHD. Radiotherapy for breast cancer as delivered in the 1970s has been associated with increased risk of CVD (34), and to refrain from smoking may reduce this risk. On the other hand, interventional diagnosis and treatment of CVD increase obviously exposure of radiation dose and cancer risk. Therefore, we should try to find novel methods which resulted in significant reductions in patient radiation dose and cancer risk, for example, dual-source CT coronary angiography.

CVD has a raised and potentially modifiable or non-modifiable risk of cancers. Hypertension is a known risk factor for renal cell carcinoma (RCC), the role and biological mechanisms of hypertension in RCC related to common genetic variants of angiotensinogen (AGT), particularly those in the promoter, which increased RCC risk among subjects who are hypertensive or overweight (35). Apolipoprotein E (ApoE) genotypes associated with increased risk of CHD, may influence development of colon cancer among those who are older at diagnosis (36).

Besides, the MetS is not only associated with increased risk of T2DM and CHD, but also with breast cancer, due primarily to the same RFs. Androgen deprivation therapy in patients with prostate cancer is commonly associated

Table 1 Mechanisms of CDC strips involved single or multiple risk factors (RFs)

E(e)SEED-BasED	Lifestyles	Main RFs
E(e)	Environment	WAS pollutions, irradiation, lower income and social status, self-diseases: such as acute or chronic infection, etc.
S	Sleeping	Insomnia, stay up later; OSA, etc.
E	Emotion	Stress, depression, etc.
E	Exercise	Physical inactivity, setting for a long time, overweight, obese, etc.
D	Diet	Unhealthy diet, active or passive smoking, dead drunk, poor nutrition, reuse of cooking oil, salt intake (>6 g/day), etc.
B	Behavior	Drug addiction, gambling, overflow sexual life, etc.
/a	Age (38,39)	Age, aged, no healthcare, etc.
/s	Safety	Unexpected events: traffic crash, drown, electric shock, fall, etc.
	Sex (39)	Male or female, divorced, bereft of one's spouse, lonely, etc.
	Study	Not study, not thinking, lack of medical knowledge, etc.
E	Education (40)	Lower education, lack of knowledge, etc.
	Employment	Unemployed, high risk occupation (e.g., IT, account), etc.
	Ethnic	The Black, epidemic region, etc.
D	Disease	A positive family history, such as AS; hypertension; CHD; DM, etc.
		Abnormal index, such as GFR (41); ABI (42); CIMT (43,44), etc.
		Precancerous pathogenesis (45), etc.
	Drug	Adverse drug effects, no herbs, no Traditional Chinese medicine, etc.

All of these RFs, standard, common, classic, single or multiple modifiable (lifestyle related) or non-modifiable (genetic), confer significant risk for developing CVD, DM, cancer, even CDC strips. General or specific RFs screening recommendations for CDC strips are outlined. In addition, E(e)SEED-BasED, healthy lifestyles were named for Hu's healthy lifestyles (HHL). WAS, water-air-sound; OSA, obstructive sleep apnea; AS, ankylosing spondylitis; CHD, coronary heart disease; DM, diabetes mellitus; GFR, glomerular filtration rate; ABI, ankle brachial index; CIMT, carotid intima media thickness; CVD, cardiovascular disorder.

with CVD, obesity, MetS and DM (37). An increased risk of RCC has been reported in subjects with hypertension and a history of DM.

From all above, due to CVD, DM and cancers linked, each other, and as co-morbid diseases, the authors think that there are actually CDC strips and named them firstly. And, the authors think that OOH syndrome is a high risk status and easy to develop CDC strips.

CDC strips: mechanisms and classifications

Here, the authors explore related mechanisms on CDC strips with several novel conceptual breakthrough, classifications (total strips, Branches/type A and main strips/type B) and clinical significance.

Mechanisms

As acquired diseases, minorities of CDC strips are related to genetic factors. The development of most of CDC strips was related mainly to lifestyles, which involved mechanisms of multi-pathways and multi-targets. On the one hand, the shared common main RFs including unhealthy lifestyles (here we mean them "Bad SEED") may link for the development of CDC strips (*Table 1*). These RFs, which related to "E(e)SEED-BasED" healthy lifestyles developed in our previous works (5-7), and named for Hu's healthy lifestyles (HHL), include environmental factors: water-air-sound (WAS) pollutions, irradiation, stress, lower social status and economic income, etc; sleep factors: insomnia, OSA; emotion factors: depression, nervous, psychological disorders; exercise factors: physical inactivity, sitting too much; dietary factors: tobacco use, harmful use of alcohol, and unhealthy diet (water, vegetable and fruits intake not enough, but red meat intakes over), etc, as well as other factors, such as age, sex, education, disease and drug. On the other hand, the shared common RFs including a positive history of family related genetic factors (here we mean them

Table 2 Mechanisms of CDC strips involved multi-pathways and multi-targets

Mechanisms of CDC strips	Pathways and targets
Organ & tissue-based (e.g., vascular-specific)	Lifestyles risk factors (*Table 1*): → Immunity function (–) → Acute or chronic inflammation → Vascular endothelial cells (VEC) injure → Vascular injure → AS or stiff or rupture → Ischemia or oxygen not enough → Microcirculation dysfunction → Organ or tissue injure → NCDs (CVD, DM, cancer, even CDC strips) → Others
Cell-based	Internal or external stimuli → inflammation Cells including: TAM, mast cells, dendritic cells, NK cells, neutrophils, eosinophils and lymphocytes Cytokines, chemokines, transcription factors, etc: (+) Including: ROS & RNS, MMP, TNF, IL-1, I-L6, IL-8, IFNs, NF-κB, etc. Enzymes, such as COX-2, LOX-5, PLA2, etc. Biomarkers, such as vitamin D, Vit E and Vit C levels, hs-CRP, MAU, Hcy, Homocysteine, CA125, CA19-9, and CA153, etc. Signals, such as SMAD, STAT3, AMPK, etc. Apoptosis Telomerase (+) CSC and (–) adults SC (46) Others, such as eicosanoid, kinins, etc.
Gene-based	A positive family history Genetic variants Gene mutation DNA repair DNA methylation Micro-RNA Others: P53, Bcl-2, etc.

Lifestyles risk factors (showed in *Table 1*) mean "Bad SEED"; genetic risk factors mean "bad soil". The shared "Bad SEED"+/– "bad soil" leading to "internal environment injure, abnormal, or unbalance" [e.g., (+) CSC and/or (–) adults SC?] may explain the mechanisms of CDC strips involved multi-pathways and multi-targets. Here, - means decrease or inactivate; + means increase or activate. TAM, tumor-associated macrophages; NK, natural killer; ROS, reactive oxygen; RNS, nitrogen species; MMP, matrix metalloproteinase; TNFα, tumor necrosis factor α; CVD, cardiovascular disorder; DM, diabetes mellitus; CRP, C-reactive protein; NcDs, non-communicable diseases; interleukins (IL-1, IL-6, IL-8), interferon (IFNs), cyclooxygenase-2 (COX-2), lipooxygenase-5 (LOX-5), phospholipase A2 (PLA2), transcription factors nuclear factor κB (NF-κB); STAT3, signal transducers and activators of transcription-3; CSC, cancer stem cell.

"bad soil"). Therefore, we think that "Bad SEED" +/– "bad soil" Theory or Doctrine on CDC strips may explain this phenomenon of co-morbid diseases. Actually, it's due to "internal environment injure, abnormal or unbalance" in human body resulting from the role of RFs related multi-pathways and multi-targets, which including organ & tissue (e.g., vascular-specific), cell and gene-based mechanisms (*Tables 1*,*2*, *Figure 1*), for example, it may activate cancer stem cells (CSCs), according to the update verified CSC hypothesis (46), and/or inactivate adults stem cells (SCs).

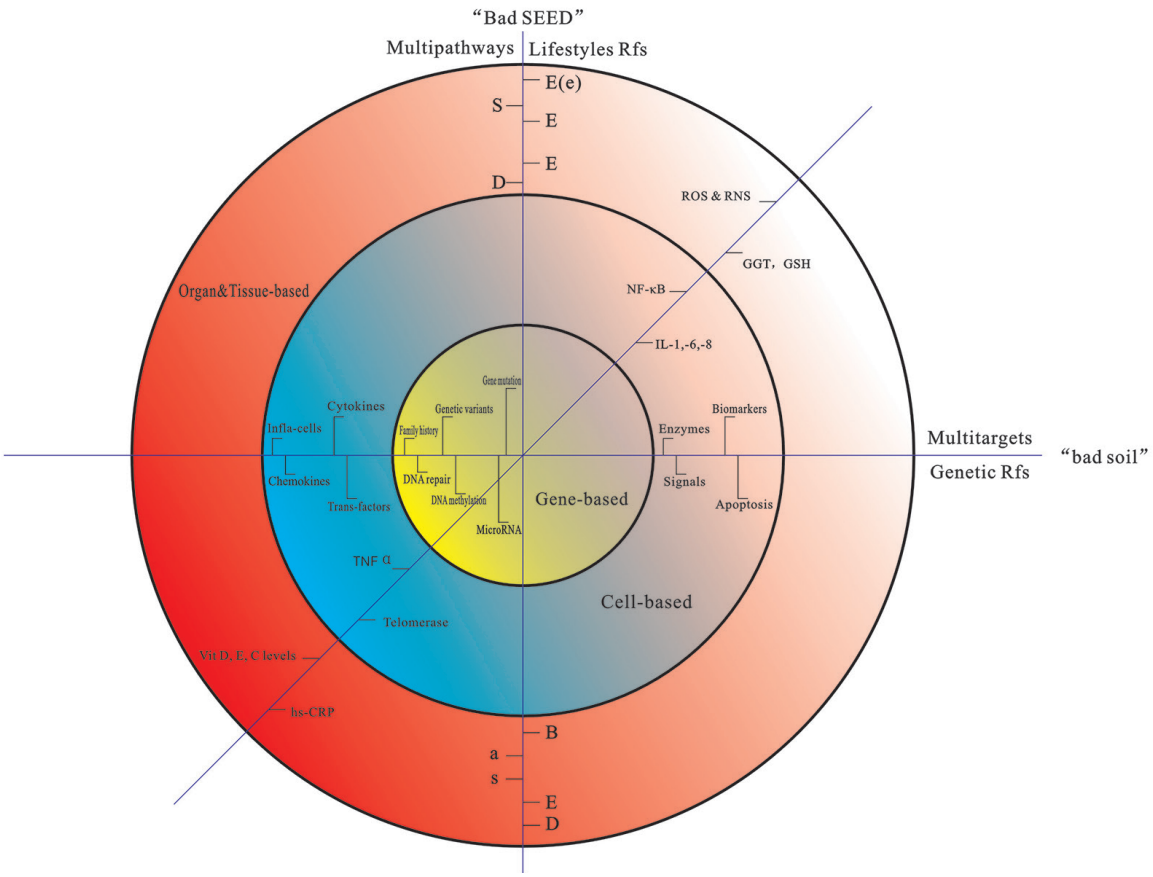

Figure 1 Mechanisms on CDC strips: "Bad SEED" +/- "bad soil" Theory or Doctrine, which involved organ & tissue (e.g., vascular-specific), cell and gene-based multi-pathways and multi-targets. Here, "Bad SEED" means abnormal E(e)SEED-BasED lifestyles which including related RFs; "bad soil" means related genetic RFs, such as family history, gene mutation, etc. These lead to "internal environment injure, abnormal or unbalance", and finally to CDC strips. RFs, risk factors.

Table 3 Classifications of CDC strips: their mains (type B) and branches (type A)

Total CDC strips	Cv(a)-DM-Ca(v) strips
Main strips (type B)	1 Cv-DM-Ca
	2 Ca-DM-Cv
	3 DM-Cv-Ca
	4 DM-Ca-Cv
	5 Cv-Ca-DM
	6 Ca-Cv-DM
Branch (type A)	1 Cv-DM or DM-Cv
	2 Ca-Cv or Cv-Ca
	3 Ca-DM or DM-Ca

Ca, cancer; Cv, cardiovascular; CVD, cardiovascular disease; DM, diabetes. Total CDC strips mean Cv(a)-DM-Ca(v) strips; CDC strips consist of linked CVD, DM and Ca, each other.

Classifications

Among CDC strips, there are three different but linked diseases, CVD, T2 or T1 DM, and cancers. Each patient may be diagnosed firstly one kind of diseases, e.g., CVD, DM or cancer. Sometimes, two or three diseases are diagnosed at the same time due to the shared RFs and not physical examination in time. Therefore, there are 3 pairs of branches (type A, *Table 3*, *Figure 2A*), which including Cv-DM or DM-Cv, Ca-Cv or Cv-Ca, and Ca-DM or DM-Ca, and 6 main strips (type B, *Table 3*, *Figure 2B*), which including Cv-DM-Ca, Ca-DM-Cv, DM-Cv-Ca, DM-Ca-Cv, Cv-Ca-DM, Ca-Cv-DM, according to the onset time of each disease. But in fact, there is often first vascular injure or pathogenesis (e.g., Chronic inflammation or AS is a common and basic factor) in most of patients, then

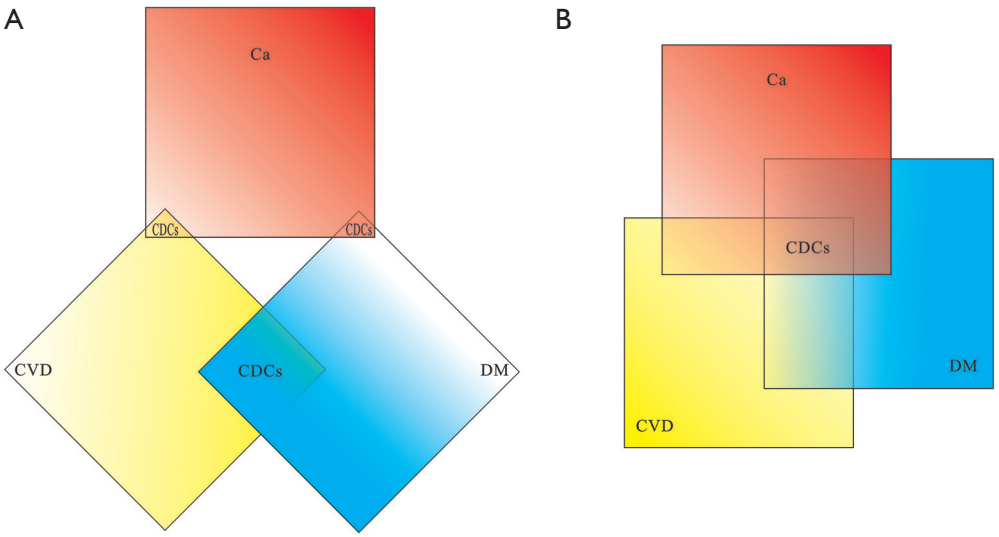

Figure 2 (A) There are three pairs of branches (type A) in CDC strips, which including Cv-DM or DM-Cv, Ca-Cv or Cv-Ca, and Ca-DM or DM-Ca, according to the onset time of each disease; (B) there are six main strips (type B), which including Cv-DM-Ca, Ca-DM-Cv, DM-Cv-Ca, DM-Ca-Cv, Cv-Ca-DM, Ca-Cv-DM, according to the onset time of each disease.

other pathogenesis. That is to say, the initial and progress of CDC strips are often from vascular tissues and involved three kinds of diseases, which including CVD, DM and cancer. So, we think Cv(a)-DM-Ca(v) strips are total strips (*Table 3*, *Figure 2A,B*). Obviously, branches of CDC strips just involved two diseases.

CDC strips: significances and prospects

As the novel conceptual breakthrough, clinical significance of CDC strips is obvious and very helpful. First, to develop new warnings, CDC strips we discovered and named may remind us of paying more attention to early detection, early prevention and early intervention of these diseases, halting the development of CDC strips; CDC strips help us understand that early prevention is the best treatment and the most important thing, and the role of primary and secondary prevention; To treat positively and to control RFs before main or branch strips are formed. Second, to create novel theories or doctrine on CDC strips—"bad SEED" +/– "bad soil" leading to "internal environment change, abnormal or unbalance"; To give new concepts on CDC strips, such as, main or branch strips, and total strips; To explore organ & tissue-based (e.g., vascular-specific pathology), cell and gene-based mechanisms on CDC strips resulting from multi-pathways and multi-targets. Third, to conduct and verify interventional effects of novel strategies we developed, such as RT-ABCDEF strategy, intervention with SEED, E(e)SEED, or E(e)SEED-BasED, that is to say, SEEDi, E(e)SEEDi, or HHLi.

All in all, the concepts, mechanisms, and classifications of CDC strips may help us to understand these NCD, prevent and control these common and high risk strips. As Chinese famous cardiologist Academician Run-Lin Gao said, "By the best and perfect prevention, CHD will disappear in the future". Of course, we think CDC strips are also included. And just as the famous professor and editor-in-chief of New England Journal of Medicine, Dr. Jeffrey M. Drazen said, "Smoking leads to cancer, heart disease and chronic obstructive lung disease. Once a smoker quits, there are substantial health benefits. It is never too late to stop smoking". Indeed, because smoking is also related with T2DM (47), we can say that smoking is the very common RFs leading to CDC strips. The earlier one stops smoking, the better it benefits one's health. It's better to stop smoking before the development of main or branch of CDC strips. In addition, chronic respiratory diseases, often caused by tobacco consumption, are considered as major NCDs that cause great mortality worldwide. In many cases, respiratory diseases, CVD, DM, and cancer are listed as "big four" NCDs. Hence, we think that "CDC strips" are the first strips among NCDs, we may promote the concept of "Re-CDC strips" in the next step as the second strips, which include Respiratory diseases. We also think it's time for us to take acts for preventing or halting CDC strips in the globe. On the one hand, we need to find

new targets for CDC strips; On the other hand, we need to develop novel targeted drugs or therapies to prevent or halt CDC strips which have the role of "a stone for three birds". At the same time, we definitely should pay more attention to their safety, efficacy and stability (48), which just like that in gene therapy. In fact, according to up-to-date global status report on NCDs released by WHO on 15 May 2014, many countries are experiencing a rapid rise in obesity among infants and children under 5 years of age. More than 40 million children under the age of 5 were overweight or obese in 2012, and 70 million children under 5 will be overweight or obese by 2025 if current trends continue. Thus, tackling childhood obesity now represents an important opportunity to reduce the development and impact of CDC strips in future—while immediately improving the health of children.

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