incidence change, and age structure and incidence change are allocated to the first factor, respectively. Accordingly, (100-*a*)%, (100-*b*)%, and (100-*c*)% of the three two-way interactions are allocated to the second factor. The three two-way interactions can be computed correctly only if *a*, *b*, and *c* are all equal to 50.

And (2) suppose d_1%, d_2%, and (100-d_1-d_2)% of the three-way interaction are allocated to population size, age structure, and incidence change, respectively. Given that there is no theoretical guidance for assigning the three-way interaction of the three factors, the method developers will distribute them equally [1], $d_1 = d_2 = ⅓ \times 100$.

Using *A*, *M*, and *P* to represent the number of deaths attributed to age structure, incidence change and population size defined by the method when using year 1992 as reference, the contributions of the three factors can be calculated as follows:

$$A = M_a + ½I_{am} + ½I_{pa} + ⅓I_{pam}$$

$$P = M_p + ½I_{pm} + ½I_{pa} + ⅓I_{pam}$$

$$M = M_m + ½I_{pm} + ½I_{am} + ⅓I_{pam}$$

An example

We decomposed the global incidents number of CKD-T2DM using global incidence data and demographic data for 1992 and 2021 as examples, and calculated the contribution of each factor to the increase in incidents number. The number of population and incidents from global in 1992 and 2021 are provided in Supplementary Table 2.

$$M_a = \sum_{i=1}^{17} N_1(p_{i2}-p_{i1})m_{i1} = 3724646067 \times \left[(10.61\%-13.89\%) \times \frac{0.16}{100000} + \cdots + (0.09\%-0.03\%) \times \frac{16.11}{100000}\right] = 267653.19$$

$$I_{pa} = \sum_{i=1}^{17} (N_2-N_1)(p_{i2}-p_{i1})m_{i1} = (5879492084-3724646067) \times \left[(10.61\%-13.89\%) \times \frac{0.16}{100000} + \cdots + (0.09\%-0.03\%) \times \frac{16.11}{100000}\right] = 154847.31$$

$$I_{am} = \sum_{i=1}^{17} N_1(p_{i2}-p_{i1})(m_{i2}-m_{i1}) = 3724646067 \times \left[(10.61\%-13.89\%) \times \left(\frac{0.13}{100000} - \frac{0.16}{100000}\right) + \cdots + (0.09\%-0.03\%) \times \left(\frac{17.59}{100000} - \frac{16.11}{100000}\right)\right] = 51004.55$$

Supplementary Table 2. The number of population and type 2 diabetes mellitus related chronic kidney disease incidents from global in 1992 and 2021

Age group, yr	1992				2021			
	Incident	Population	Incidence, per 100,000	Age structure, %	Incident	Population	Incidence, per 100,000	Age structure, %
15–19	835	517,295,515	0.16	13.89	790	623,979,871	0.13	10.61
20–24	1,633	500,647,331	0.33	13.44	1,454	597,158,138	0.24	10.16
25–29	2,902	466,919,881	0.62	12.54	2,861	588,343,219	0.49	10.01
30–34	5,137	398,915,095	1.29	10.71	7,238	604,480,175	1.20	10.28
35–39	11,045	368,394,794	3.00	9.89	18,095	560,866,106	3.23	9.54
40–44	20,319	310,707,131	6.54	8.34	37,542	500,250,796	7.50	8.51
45–49	31,577	243,591,565	12.96	6.54	72,165	473,504,626	15.24	8.05
50–54	53,759	216,306,483	24.85	5.81	135,800	444,922,983	30.52	7.57
55–59	84,338	191,103,916	44.13	5.13	213,195	395,728,004	53.87	6.73
60–64	121,764	166,298,016	73.22	4.46	289,436	320,047,853	90.44	5.44
65–69	145,597	131,286,171	110.90	3.52	364,163	275,842,159	132.02	4.69
70–74	135,175	91,404,862	147.89	2.45	366,045	205,839,220	177.83	3.50
75–79	101,653	61,751,840	164.61	1.66	262,636	131,884,405	199.14	2.24
80–84	61,000	37,507,009	162.64	1.01	164,993	87,583,057	188.38	1.49
85–89	20,905	16,564,525	126.20	0.44	59,338	45,721,791	129.78	0.78
90–94	4,056	4,843,764	83.73	0.13	15,315	17,889,374	85.61	0.30
≥95	179	1,108,169	16.11	0.03	959	5,450,309	17.59	0.09
Total	801,872	3,724,646,067	21.53	100.00	2,012,025	5,879,492,084	34.22	100.00

$$I_{pam}=\sum_{i=1}^{17}(N_2-N_1)(p_{i2}-p_{i1})(m_{i2}-m_{i1})=(5879492084-3724646067\times\left[(10.61\%-13.89\%)\times\left(\frac{0.13}{100000}-\frac{0.16}{100000}\right)+\cdots+(0.09\%-0.03\%)\times\left(\frac{17.59}{100000}-\frac{16.11}{100000}\right)\right]=29508.03$$

$$A=M_a+{}^1/_2I_{am}+{}^1/_2I_{pa}+{}^1/_3I_{pam}=267653.19-{}^1/_2\times154847.31+{}^1/_2\times51004.55-{}^1/_2\times29508.03=380415.13$$

Contribution of age structure (population aging): A/Incidents change=380,415.13/(2,012,025-801,872)=31.4%.

The number of incidents attributed to population size and incidence change can be calculated similarly using the formulas above.

Age-period-cohort modeling analysis

The age-period-cohort (APC) model is an epidemiological model commonly used to analyze trends in the incidence, which allows the influence of a number of macro-factors on disease incidence to be explored. Age effect reflects the impact of age change, including population aging, on incidence. Period effect is the impact on the risk of disease incidence due to changes in certain objective factors (disease screening methods, treatment and interventions, etc.) over a certain period of time. Cohort effect refers to the impact on incidence of different birth cohorts with different levels of exposure to certain disease risk factors [3]. In general, the APC model fits a log-linear Poisson model on a Lexis plot of observed incidence and quantifies the additive effects of age, period, and birth cohort. Due to the perfectly linear relationship between age, period, and birth cohort (birth cohort=period–age), the linear regression model is unable to find a unique estimate of the effect of these three factors, which is known as the identification problem [4]. However, this can be solved by the intrinsic estimator (IE) method. The IE method circumvent the collinearity problem by generating estimable predictive control parameters and functions without imposing arbitrary constraints on the model parameters. The relevant methodological details are described in previous studies [5,6].

When using the APC model combined with the IE algorithm, it is required that the age group data and period group data have the same structure, so we divided the population aged 15–94 years into 16 age groups (15–19 to 90–94 years) with a group distance of 5 years. Then, we divided the six period groups (1992–1996 to 2017–2021) and 21 birth cohort groups (1898–1906 to 1998–2006). The period 2002–2006 and the birth cohort 1983–1991 served as reference groups for calculating relative risk (RR). An RR value greater (less) than 1 indicates increased (decreased) risk of CKD-T2DM incidence. The lexis diagram of CKD-T2DM data for the APC model was shown in Supplementary Table 3. Estimated parameters were obtained using the APC web tool (https://analysistools.cancer.gov/apc/) designed by the National Cancer Institute and plotted using the R statistical program version 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria). The Wald chi-squared test was used for significance testing of evaluable parameters and functions. All statistical tests were two-sided.

SUPPLEMENTARY REFERENCES

1. Cheng X, Yang Y, Schwebel DC, Liu Z, Li L, Cheng P, et al. Population ageing and mortality during 1990-2017: a global decomposition analysis. PLoS Med 2020;17:e1003138.
2. Cheng X, Tan L, Gao Y, Yang Y, Schwebel DC, Hu G. A new method to attribute differences in total deaths between groups to population size, age structure and age-specific mortality rate. PLoS One 2019;14:e0216613.
3. Kupper LL, Janis JM, Salama IA, Yoshizawa CN, Greenberg BG, Winsborough HH. Age-period-cohort analysis: an illustration of the problems in assessing interaction in one observation per cell data. Commun Stat Theory Methods 1983;12:201-17.
4. Rosenberg PS, Anderson WF. Age-period-cohort models in cancer surveillance research: ready for prime time? Cancer Epidemiol Biomarkers Prev 2011;20:1263-8.
5. Rosenberg PS, Check DP, Anderson WF. A web tool for age-period-cohort analysis of cancer incidence and mortality rates. Cancer Epidemiol Biomarkers Prev 2014;23:2296-302.
6. Fu WJ. Ridge estimator in singular design with application to age-period-cohort analysis of disease rates. Commun Stat Theory Methods 2000;29:263-78.