Stroke incidence and 30-day and six-month case fatality rates in Udine, Italy: a population-based prospective study

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Background **Stroke incidence in high-income countries is reported to decrease, and new data on stroke incidence and outcome are needed to design stroke services and to ameliorate stroke management.**

Methods **This study is part of a two-year prospective community-based registry of all cerebrovascular events in the district of Udine (153 312 inhabitants), Friuli-Venezia Giulia region, northeast of Italy, between 1 April 2007 and 31 March 2009. Overlapping sources for case finding were used, combining hot and cold pursuit.**

Results **We identified 784 stroke cases, 640 (81·6%) incident. The crude overall annual incidence rate per 100 000 residents was 256 (95% confidence interval 241–271) for all strokes and 209 (95% confidence interval 195–223) for first-ever strokes. Incidence rate for first-ever strokes was 181 (95% confidence interval 155–211) after adjustment to the 2007 Italian population and 104 (95% confidence interval 88–122) compared with the European standard population. Incidence rates for first-ever strokes was 215 (196–235) for women, 202 (183–223) for men. Crude annual incidence rates per 100 000 population were 167 (153–178) for ischemic stroke, 31 (26–37) for intracerebral hemorrhage, 8·1 (5·7–11·4) for sub-arachnoid hemorrage, and 4·6 (2·8–7·1) for undetermined stroke. Overall case fatality rates for first-ever stroke were 20·6% at 28 days and 30·2% at 180 days.**

Conclusions **Our study shows incidence rates higher than previously reported in our region but not supporting the view of higher incidence rates in Northern than in Southern Italy. Results contribute to time-trends analysis on epidemiology, useful for dimensioning services in Italy and show the persistence of a gap between the outcome of stroke in Italy and that of the best performing European countries, urging to adopt better stroke management plans.**

Key words: epidemiology, intracerebral hemorrhage, ischemic stroke, stroke, stroke sub-types, vascular events

Introduction

Stroke is the second leading cause of death and the first cause of long-term neurological disability in adults (1). During the last four decades, from 1970 to 2008, age-adjusted stroke incidence rates decreased by 42% in high-income countries (from 163 per 100 000 person years in 1970–79 to 94 per 100 000 person years in 2000–08; $P = 0{\cdot}0004$), whereas in low- to middle-income countries, the stroke incidence rates were more than doubled during the same time interval (from 52 per 100 000 to 117 per 100 000 person years; $P < 0{\cdot}0001$) (2). These data suggest that stroke incidence and burden may change over time and across different regions worldwide.

In Italy as well, according to a recently published review (3) on epidemiology of stroke, the incidence rate adjusted to the Italian population spread over a wide range, between 183 and 311 per 100 000 population-years, depending on different registries. In Friuli-Venezia Giulia, a region of 1 216 016 inhabitants, located in the northeastern part of the country, stroke incidence had been the subject of three previous community-based studies (4–6). Two studies had the limit to analyze only intermediate age groups: between 35 and 74 years in the study by Palmieri *et al.* (4) and between 35 and 64 years in the World Health Organization (WHO) Monitoring trends and determinants in cardiovascular disease (MONICA) project register (5). In the other one, by Francescutti *et al.* (6), the method of stroke ascertainment included only a cold pursuit, such as analysis of hospital discharge records.

Our study tried to overcome these limitations, using the most up-to-date recommendations (7–9) to obtain better quality and comparable data on stroke events in our region, aiming to contribute at defining time-trend and regional differences in stroke incidence and case fatality in Italy.

Subjects and methods

The present study on stroke incidence and early outcome is part of a population-based study on the incidence and outcome of all cerebrovascular diseases in the district of Udine, Friuli-Venezia Giulia region, northeast of Italy. Being an observational study, diagnostic procedures and clinical management of patients were not dictated by a specified protocol but rather delivered according to the practice of the treating physician. The study was approved by our local Ethics Committee.

Standard definitions

According to the WHO definition, stroke was defined as an acute onset of symptoms and/or signs of focal disturbance of cerebral function lasting >24 h or leading to death, presumed, after exclusion of other causes, to be due to vascular disease (10,11). Patients who received thrombolysis were diagnosed as stroke even if symptoms are completely resolved within 24 h. Incident stroke was defined as a first-ever-in-a-lifetime (FES), occurring within the study period and with no clinical history of previous stroke.

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Stroke sub-types were classified in three major sub-groups: (i) ischemic stroke (IS), due to the sudden occlusion, thrombotic or embolic, of a cerebral artery; (ii) intracerebral hemorrhage (ICH), when bleeding into the brain tissue was detected; and (iii) sub-arachnoid hemorrhage, characterized by bleeding into the sub-arachnoid space. Sub-type was assigned according to clinical data, confirmed by brain imaging results. Stroke cases that did not undergo imaging were classified as undetermined.

High blood pressure (HBP) was defined as systolic pressure ≥140 mmHg and/or diastolic pressure ≥90 mmHg, and/or use of antihypertensive medication, and/or being told at least twice by a physician or other health professional that one has HBP. Atrial fibrillation (AF) was diagnosed if patient had an AF in electrocardiogram (ECG) recording prior to stroke and/or during hospitalization. Carotid stenosis was defined according to TOAST criteria as narrowing of the internal carotid artery lumen of >50% on carotid duplex ultrasound or angiography (12). Diabetes mellitus was defined as history of diabetes that was confirmed in medical records and/or use of insulin/oral hypoglycemic agents, and/or random nonfasting blood glucose concentration ≥11·1 mmol/l (200 mg/dl). Hypercholesterolemia was defined as fasting total cholesterol serum level ≥5·18 mmol/l (200 mg/dl) and/or fasting Low density lipoprotein (LDL) cholesterol serum level of ≥4·14 mmol/l (160 mg/dl) and/or use of lipid-lowering medications. Coronary heart disease was defined as a history of either acute myocardial infarction or angina pectoris or coronary artery bypass graft or percutaneous coronary intervention. Patients were defined as smokers if they were current smokers or they had stopped smoking less then three-months before the index stroke.

Study population

The population of the Udine district includes 153 312 residents (data based on the 2007 census analysis) (13), 80 349 women and 72 963 men. We attempted to ascertain all cases of incident or recurrent strokes occurring between 1 April 1 2007 and 31 March 31 2009. Prior to start the formal ascertainment, we completed a test run of one-month to improve the case finding process. Ascertainment continued for three-months after 31 March 2009 to identify patients presenting late with a stroke or a transient ischemic attack (TIA) that might have occurred on or before 31 March 2009. Case ascertainment included patients who had an event while temporarily away from Udine district. Patients visiting to Udine who were not resident were excluded.

Study criteria

We followed the criteria for an ideal population-based stroke study, as they were already reported and revised by different authors in the past decade (7–9). Multiple overlapping sources for case finding were used, combining hot and cold pursuit.

Hot pursuit included: daily review of hospital and emergency department admission registers; daily review of all patients referred to neuroradiology and neurosonology services; daily assessment of admission to cardiology, emergency, medicine, neurology, ophtalmology, stroke, and vascular surgery wards; and general practitioners' (GPs) referrals of all possible TIAs and strokes to the 24-h open-access outpatient clinic for neurological emergency of our department.

Cold pursuit included: monthly review of hospital discharge records; monthly contacts with rehabilitation services; quarterly phone contacts with GPs; and six-monthly review of death certificates.

A more complete description of study population, case ascertainment, and definitions has been previously reported in an article on TIA incidence, recently published (14).

Patients' evaluation and follow-up

Patients were assessed by a study neurologist within 24 h if admitted to our neurology ward, within 48 h if admitted to other departments, and within two-weeks if not hospitalized. Patients were then evaluated at one- and six-months from index event. All participants signed an informed consent at the time of the interview. If needed, the principal caregiver of the subject enrolled in the study signed the informed consent.

Data collection concerned event characteristics, demographic issue, risk factors, and diseases. The subjects were asked to report any use of prescription drugs. Hospital and outpatients records were reviewed to obtain a confirmation of the self-reported diagnosis and of the drug prescriptions. In patients who were dysphasic or died prior to assessment, information was obtained by relatives, GPs, hospital records, and/or death certificates.

Statistical analysis

Stroke cases were categorized as FES or recurrent. Only FESs were included in the present analysis. Incidence is reported for FES and for all stroke sub-types as crude rates (per 100 000/year) and age-standardized rates to the 2007 Italian population analysis (13) and to the European standard population (15). The denominator for the calculation of incidence was obtained approximately by multiplying the average size of the study population by the length of the study period (16). The 95% confidence interval (CI) were calculated assuming a Poisson distribution for the number of events. Categorical variables are expressed in percentage. Continuous variables are expressed as mean ± standard deviation (SD) and median. An unpaired *t*-test was used to compare age sub-groups. Data were analyzed using SPSS 13·0 (IBM corporation, New York, US, release: 1st sept 2004).

Results

During the study period, we identified 784 stroke cases, 640 FESs (81·6%), and 144 (18·4%) recurrent events, of whom 735 (93·8%) were hospitalized. Baseline characteristics of FES patients, including risk factors and drug treatments prior to stroke onset, are all listed in Table 1. Six hundred five (605) out of 640 FESs (94·5%) were hospitalized. Brain imaging was performed in 623/640 (97·3%) of FES patients, 622 patients underwent a computed tomography (CT) scan, 40 patients underwent both a CT and an MRI scan, and one patient had only an MRI. Three more patients, with central retinal artery occlusion, underwent only a fluoroangiography, and they were than classified as IS.

Mean age of FES patients was 76·2 (median 79·0; SD 13·8), women were 53·9% and were significantly older than men (79·2 vs. 72·7; $P < 0·001$).

Age- and gender-specific incidence rates with 95% CI are shown in Table 2. The crude overall incidence rate per 100 000 persons year was 209 (195–223); rates were 181 (155–211) when adjusted to the 2007 Udine district population (13) and 104 (88–122) compared with the European standard population (16).

Incidence rates increased with age both in men and in women, with highest incidence rates in the over-85-year age group (Table 2). FES incidence was 215 (196–235) in women and 202 in men (183–223). The proportion of different FES sub-types and their incidence rates are reported in Table 3. Case fatality rates for stroke sub-types are presented in Table 4.

Table 1 Baseline characteristics of the 640 first-ever strokes included in the study

	Mean/median (SD) or N (%)
Age (years)	76·2/79 (13·8)
Female gender	345 (53·9)
Hospitalized patients	605 (94·5)
Brain CT	623 (97·3)*
Brain MRI	41 (6·4)
tissue Plasminogen Activator (tPA) given (506 IS only)	12 (2·4)
Risk factors	
Hypertension	491 (76·8)
Atrial fibrillation	208 (32·5)
Diabetes	142 (22·2)
Hypercholesterolemia	140 (21·9)
Coronary heart disease	130 (20·3)
Current smoker	84 (13·1)
Symptomatic carotid stenosis >50%	82 (12·9)
Peripheral artery disease	48 (7·5)
Previous TIA	44 (6·9)
Drug treatment (prior to the event)	
Antihypertensive	275 (43·0)
Antiaggregant	217 (33·9)
Antidiabetic	82 (12·8)
Anticoagulant	76 (11·9)
Hypolipidemic	72 (11·3)

*40 of them underwent also MRI scan.
SD, standard deviation; N, number of cases; CT, computer tomography; MRI, magnetic resonance imaging; IS, ischemic stroke; TIA, transient ischemic attack.

Considering TOAST distribution among FES, it is noteworthy that among all 506 FESs (50·4%) patients remained without a definite etiology (considering altogether the 'incomplete evaluation', the 'negative evaluation', and the 'more than on possible cause' categories), of which 33·8% is due to an incomplete evaluation. Figure 1 shows that, in patients admitted to neurology (293/506), the percentage of 'nondefinite cause' category is 35·2% (15·7% is due to an incomplete evaluation); in those, instead, admitted to non-neurological wards (187/506), this proportion rises up to 71·6% (59·9% is due to an incomplete evaluation).

Discussion

Several epidemiological studies on stroke incidence and prognosis were published in Italy in the last two to three decades. However, according to a recent meta-analysis (3), just few of them cover all, or at least most, of the defined criteria for ideal population-based stroke studies; moreover, these few studies show various items of heterogeneity, among which: (i) dispersion over a wide time span; (ii) inclusion of several regions with different health systems and standards of care; and (iii) different population sizes, sometimes with small samples of stroke cases. In the region Friuli-Venezia Giulia, previous studies had even deeper methodological limitations, as they only used hospital discharge records (cold pursuit) to ascertain stroke events, they did not distinguish between different stroke sub-types or they concentrated their analysis on the part of population <75 or <65 years old. Their limitations preclude the possibility of a real comparison with our results. However, Francescutti *et al.* (6), 10 years before us, tried to estimate FES incidence using data from a population-based health information system (a cold pursuit only) in all age groups but excluding nonhospitalized patients: They found a standardized incidence rate of 135/100 000/year (no CI provided), somewhat lower than our 181/100 000/year (CI 155–211). We believe that our results are reliable because our study meets the criteria for 'ideal' population-based stroke studies (7,10–12), and strong efforts were made to ensure completeness of case ascertainment: a redundant overlapping approach with a mixed cold and hot pursuit was used (7). This method led to the exclusion of 1150 cases with suspected stroke: 175 were TIAs and 975 had an alternative diagnosis (14).

Table 2 Age- and gender-specific annual incidence per 100 000-year population for stroke in Udine district, Italy (1 April 2007 to 31 March 2009)

Age group (years)	Total				Women				Men			
	No.	At risk	Rate	95% CI	No.	At risk	Rate	95% CI	No.	At risk	Rate	95% CI
0–44	19	153 586	12	8–18	10	75 260	13	7–22	9	78 326	11	6–20
45–54	25	42 158	59	41–83	6	21 420	28	12–55	19	20 738	92	60–134
55–64	56	41 550	135	107–168	23	22 218	103	71–147	33	19 332	171	125–228
65–74	131	35 562	368	317–426	49	19 622	250	194–317	82	15 940	514	425–618
75–84	223	24 654	904	807–1011	121	15 498	781	668–908	102	9 156	1114	939–1313
85 +	186	9 114	2041	1801–2305	136	6 680	2036	1757–2347	50	2 434	2054	1601–2600
Total	640	306 624	209	195–223	345	160 698	215	196–235	295	145 926	202	183–223
ASRI			181	155–211			180	147–222			184	146–231
ASRE			104	88–122			85	65–111			129	100–165

CI, confidence interval; ASRI, age-standardized rate, Italian population 2007; ASRE, age-standardized rate, European population.

Table 3 Crude annual incidence per 100 000 population-year for pathological sub-types of first-ever stroke (Udine district, 1 April 2007 to 31 March 2009)

	Total				Women			Men		
Stroke sub-type	% of FES	Cases/ population at risk	Rate (95% CI)	ASRE (95% CI)	% of FES	Cases/ population at risk	Rate (95% CI)	% of FES	Cases/ population at risk	Rate (95% CI)
IS	79·1	506/153 312	165 (153–178)	79·6 (79·2–80·1)	75·9	262/80 349	163 (147–181)	82·7	244/72 963	167 (150–186)
ICH	14·8	95/153 312	31 (26–37)	16·7 (16·5–16·9)	16·5	57/80 349	35 (28–44)	12·9	38/72 963	26 (19–34)
SAH	3·9	25/153 312	8·1 (5·7–11·4)	6·3 (6·1–6·4)	4·9	17/80 349	10·6 (6·7–15·9)	2·7	8/72 963	5·5 (2·7–9·9)
UND	2·2	14/153 312	4·6 (2·8–7·1)	1·7 (1·65–1·79)	2·6	9/80 349	5·6 (2·9–9·8)	1·7	5/72 963	3·4 (1·3–7·2)
Total		640/153 312	209 (195–223)			345/80 349	215 (196–235)		295/72 963	202 (183–223)

FES, first-ever stroke; CI, confidence interval; ASRE, age-standardized rate, European population; IS, ischemic stroke; ICH, intracerebral hemorrhage; SAH, sub-arachnoid hemorrage; UND, undetermined stroke.

Table 4 Case fatality rate at 28 days, three- and six-months for first-ever stroke, according to stroke sub-types

	28 days case fatality rates		90 days case fatality rates		180 days case fatality rates	
Stroke sub-type	Number of death/total	CF rate (95% CI)	Number of death/total	CF rate (95% CI)	Number of death/total	CF rate (95% CI)
IS	85/506	16·8 (13·9–20·1)	116/506	22·9 (19·5–26·7)	138/506	27·3 (23·6–31·4)
ICH	30/95	31·6 (22·7–42·8)	35/95	36·8 (27·2–48·8)	36/95	37·9 (28·1–50·0)
SAH	6/25	24·0 (10·0–47·0)	6/25	24·0 (10·0–47·0)	6/25	24·0 (10·0–47·0)
UND	11/14	78·6 (44·1–100·0)	13/14	92·9 (54·9–100·0)	13/14	92·9 (54·9–100·0)
Total	132/640	20·6 (17·8–23·8)	169/640	25·8 (23·2–30·0)	192/640	30·0 (26·5–33·8)

CF, case fatality; CI, confidence interval; IS, ischemic stroke; ICH, intracerebral hemorrhage; SAH, sub-arachnoid hemorrhage; UND, undetermined stroke.

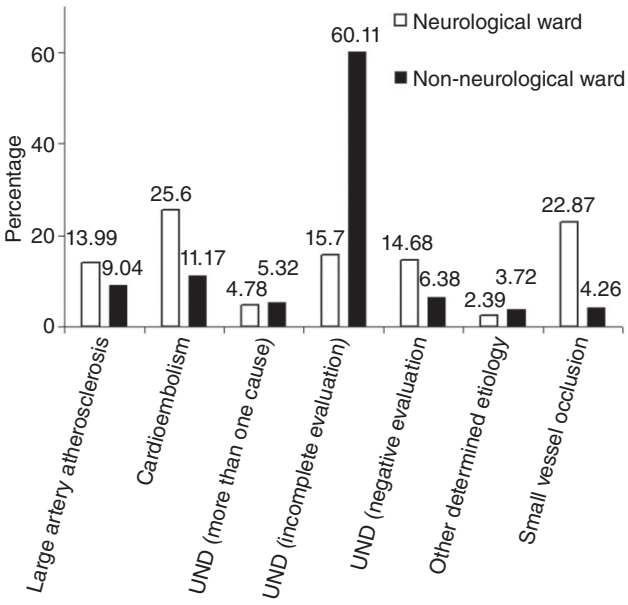

Fig. 1 TOAST distribution among FES according to the ward of admission. UND, stroke of undetermined etiology; FES, first-ever stroke.

Doubts may be raised about the use of WHO stroke/TIA definitions (10,11) as some studies suggested the opportunity of a change from a time-based definition into a tissue-based one (17). However, current stroke management in Italy does not include the routine use of advanced brain imaging in the majority of hospitals. In our study, for example, only 6·4% (41/640) of patients underwent brain magnetic resonance, the minority of them in the hyperacute phase of stroke. Thus, sometimes, 'old' definitions maybe useful still nowadays to compare different epidemiological studies.

The high crude incidence, 209/100 000/year, and low standardized rate, 104/100 000/year, compared with European population, reflect the great proportion of older age groups in our population compared with Europe. The age and gender structure of the Udine district population and the comparison among our study population, Italian and European standard ones are shown in Table 2. Our 181/100 000/year incidence rate standardized to the Italian population, even if higher than previously reported in our region, is still lower than rates reported in other northern Italy registers (3) and similar to those reported in southern Italy. This difference was already highlighted in the article by Francescutti (6) in which standardized FES incidence rate was similar to the one measured in Vibo Valentia (Calabria region, southern Italy) and much lower than the rates in Northern and Central Italy. These data may confirm the suspect that an actual lower stroke incidence exists in Friuli-Venezia Giulia compared with the other Northern Italian regions. Alternatively, we should speculate that a decrease in stroke incidence during the last decade, combined with a case undersascertainment in the previous studies, may explain our present results. With respect to this issue, in fact, all previously published registers in Italy report data from late 1980s to 2002, while more aggressive stroke preventive strategies have

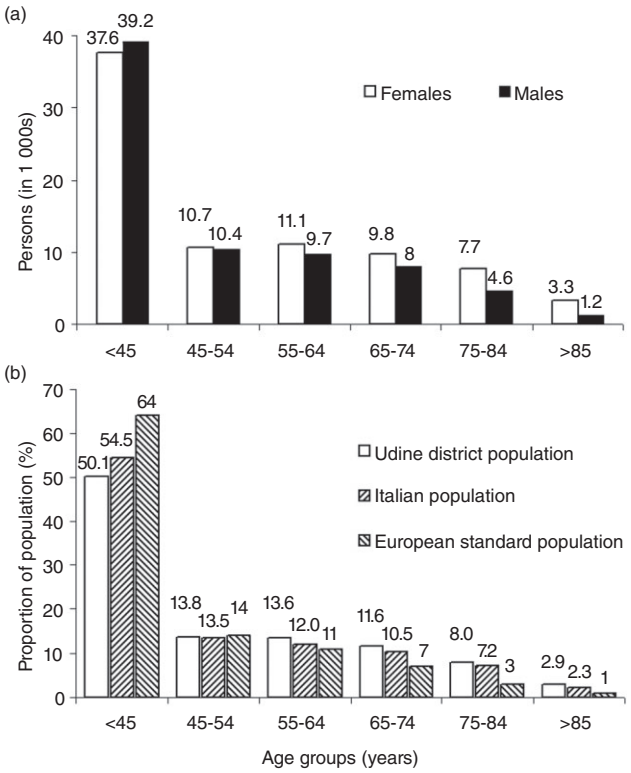

Fig. 2 (a) Age and gender structure of Udine district population, according to 2007 census analysis 13. (b) Comparison among Udine district, Italian and European standard population structures, showing higher proportion of older age groups in Udine.

become to be established, with a particular emphasis on the correction of risk factors. Further studies are needed to confirm regional differences and a time trend toward reduction of stroke incidence in Italy.

Crude gender-specific incidence rate proved higher in women than in men (Table 2); however, this is due to the different age structure of male and female population (Fig. 2), as confirmed by the specific age and gender rates. This difference, according both to C-test (the common conditional method) and to E-test (the method of testing the difference between two Poisson means based on estimated *P* values) (18) is significant for the 45–54, 65–74, and 75–84 age groups (*P* value = 0·012, <0·0001, and 0·01 with the C-test and 0·007, <0·0001, and 0·011 with the E-test).

Standardized incidence rate for ICH, 16·7/100 000 years (95% CI 16·5–16·9) was in range with data previously reported in other European studies. This support evidence that regional variations in stroke incidence are related just to differences in IS incidence (19).

TOAST distribution for first IS highlights the urgent need for a complete evaluation of stroke patients even in a neurological department. The situation is much worse in medical units. At this stage, no comparison is possible for TOAST distribution among our study and other Italian registers. In fact, to our knowledge, no data on IS etiology are available from other population-based studies in Italy and only few registers, collecting patients consecutively hospitalized, published TOAST distribution (20,21).

Case fatality rates for FES are similar to those reported in the other Italian registers more than 10 years ago, thus reflecting the still current and urgent need to improve acute stroke management in Italy. Rates reported by recent epidemiological studies in other European countries were considerably lower (13·6%, Ludwighshafen (22); 14·3% Lund (23); 10·0% Dijon (24)). It is noteworthy that our high rates were mainly because of still high case fatality in IS rather than in ICH. In fact, for ICH, 28-day case fatality was 31·6%, comparable with that observed in all the other European studies during last decade. We suggest that the still insufficient spread of dedicated acute stroke services and the low rates of patients treated with intravenous thrombolysis in Italy (only 2·4% of FES in our register) may explain, at least in part, the excess of case fatality rate related to IS in our population.

Our study has some limitations. We reviewed hospital admissions, discharge letters from other departments, and brain imaging requests; we had regular contacts with cardiologists, internists, radiologists, GPs, and residential homes; and we reviewed all emergency and death certificates. However, although unlikely, we cannot completely exclude the possibility of a limited underassessment, even if we attempted to ascertain almost all stroke cases through these multiple overlapping sources. The small proportion of patients receiving MRI could have led to underestimation of lacunar or vertebrobasilary strokes. Moreover, despite the excellent collaboration of GPs, the possibility of missed cases could belong also to nonhospitalized patients. However, hospitalization rate and rate of neuroimaging are in line with those of other recently published stroke registers (22–24), thus only a minority of patients (2·2%) were not classifiable.

Conclusions

Our study provides both complete and up-to-date data on stroke epidemiology in our region. Furthermore, it provides useful information for time-trend analysis and to highlight possible regional differences in stroke incidence in Italy. Finally the study underlines the need to plan better stroke management in Italy, in order to obtain outcomes more similar to those of the best performing countries.

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