

Supplementary Material

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Supplementary Description of Databases

The four Nordic countries, Finland, Iceland, Norway, and Sweden, have a combined population of nearly 22 million and are all cradle-to-grave welfare states with universal and tax-funded healthcare systems. All four countries have similar population-based nationwide health registers that can be linked using the personal identity number unique to all citizens. Reporting to the health registers is mandated by law and is near complete. The key registers for our study are the medical birth registers (i.e., information on live- and stillbirths, mother and child), patient registers (i.e., information on inpatient and outpatient hospital visits, diagnoses and procedures), prescription registers (i.e., information on drugs dispensed at pharmacies) and the cause-of-death registers (i.e., information on the time and cause of death).

Below is a non-exhaustive description of the registers that provided data for our study. A comprehensive review of the Nordic healthcare systems and key registers is available from Laugesen et al. (1).

Finland

The **Finnish Medical Birth Register** was established in 1987. Reporting is mandatory and registry includes data on all live births and stillbirths of at least 500 grams or 22 completed gestational weeks, as well as data on mothers.

Register of Reimbursed Drug Purchases and Register of Medical Special

Reimbursements. Nationwide databases on reimbursed drug purchases available from 1995. If an individual is entitled to special reimbursement, then drug refill is accompanied with indication for which the prescription was reimbursed.

The **Finnish Patient Register - Care Register for Health Care** contains dates of hospitalizations and visits, all diagnoses (ICD codes) and surgical procedures (NCSP codes) from inpatient stays and outpatient specialist care since 1967/1998 and primary care visits since 2011.

Finnish Register of Congenital Malformations contains all malformations (including terminations and stillbirths) identified within one year of birth and some thereafter, which have been validated based on hospital records.

Register of Primary Health Care Visits includes data collected from pilot municipalities in 2008–2009. Since 2011 the data collection has covered all outpatient primary health care delivered in Finland.

Iceland

Icelandic Medical Birth Register: Since 1981, mandatory registration of all live- and stillbirths of at least 500 grams or 22 completed gestational weeks.

Icelandic Prescription Medicines Register: Since 2003, mandatory registration of all outpatient drugs dispensed in Iceland. Prescription drugs administered to individuals in nursing homes are included from 2011 onwards.

The **Icelandic Patient Register** contains dates of hospitalizations and visits, all diagnoses (ICD codes) and surgical procedures (NCSP codes) from inpatient stays since 1999.

The **Icelandic Cause of Death Register** is a centralized national registry that is maintained by the Directorate of Health and contains mortality data for the Icelandic population, categorized according to the ICD-10 classification system. This includes data on date of death and the main underlying cause of death for each deceased individual.

Statistics Iceland: Migration (immigration/emigration), educational attainment.

Norway

Medical Birth Registry of Norway: Since 1967, mandatory registration of all live and stillbirths from 16 completed gestational weeks (12 weeks from 2002, however miscarriages below 16 weeks are incomplete). Includes all pregnancy terminations for fetal anomaly (TOPFA) since 1999.

Norwegian Prescription Database: Since January 2004, mandatory registration of all drugs dispensed in Norway. Since 2008, includes ICD-10 diagnosis for prescriptions dispensed for chronic conditions. Before 2008, another reimbursement coding system was used.

Norwegian Patient Registry: Dates, diagnoses and procedures from specialists and inpatient care since 2008.

Norwegian Cause of Death Registry: Contains data since 1951 on date and cause of death, classified according to ICD-10 since 1996.

National Education Database: Established in 1970 and updated every year. Contains information about the level of education of every Norwegian inhabitant who has received education in Norway from the age of 16 years.

Norwegian Control and Payment of Health Reimbursements Database (KUHR): The registry contains information on bills from health services, including primary care, which have been reimbursed to patients by the state. Full data are available from 2006.

Sweden

The Swedish Medical Birth Register covers since 1973, over 99% of all livebirths and stillbirths from gestational week 22. Before 1 July 2008, only stillbirths occurring after 28 gestational weeks were included. Data is collected from antenatal care clinics, delivery units and pediatric examination of the infant.

The Swedish Prescribed Drug Register was established in July 2005 and contains complete national data on all pharmaceuticals dispensed on prescription. Dispensations are recorded according to the Anatomical Therapeutic Chemical (ATC) classification system, with the date of dispensation, the strength, and quantity. Drugs administered in hospitals or nursing homes with no individual prescription and drugs sold over the counter (OTC) are not included.

The Swedish Patient Register contains dates of hospitalizations and visits, all diagnoses (ICD codes) and surgical procedures (NCSP codes) from inpatient stays. The reporting started in 1964 and since 1987, the register has covered all public, inpatient care in Sweden. Since 2001 both public and private care visits are included in the register and since 2002 there is almost full coverage of all outpatient hospital visits.

Swedish Cause of Death Register: All deaths registered in Sweden since 1952.

Longitudinal integrated database for health insurance and labour market studies (LISA): From Statistics Sweden, contains data on highest achieved education each year.

Supplementary Table 1. Definition of exclusion criteria

Exclusion criteria	Look-back	Definition	Notes
Assisted reproductive therapy (ART)	n/a	<u>MBR (not Iceland):</u> Checkbox	Defined by MBR checkbox, or ICD-10 diagnosis codes, or NCSP procedure codes, or perigestational dispensing of gonadotropin-releasing hormone (GnRH) analogue and gonadotropin and human chorionic gonadotropin (hCG) (2). Covariate in sensitivity analysis of mothers with polycystic ovary syndrome.
	LMP-90 days to delivery	<u>MBR, NPR, CDR, KUHR, PHC:</u> ICD-10: Z311, Z312, Z313, N98	
	LMP-90 days to delivery	<u>NPR (not Iceland), MBR (not Finland):</u> NCSP Finland: LCA30, TLW00, TLW10, TLW11, TLW12, TLW14, TLW20 NCSP Iceland: LBSF11, LBSF12, LCSA30, LCXA00, LCXA10, LCXA12, LCXA30, LCXA99, LGXA00, LGXA12, LGXA14, LGXA19 NCSP Norway: LBF11, LBF12, LCA30, LCW30K, LCGX10, LCGX20 NCSP Sweden: AL015, AL017, DL001, DL002, DL003, DL007, DL008, LCA30	
	LMP-90 to LMP+97 days	<u>PDR:</u> ATC: Gonadotropin-releasing hormone (GnRH): H01CA02, H01CC01, H01CC02, L02AE01, L02AE03 Gonadotropin: G03GA02, G03GA04, G03GA05, G03GA06, G03GA09, G03GA30 Human chorionic gonadotropin (hCG): G03GA01, G03GA08	
Polycystic ovary syndrome (PCOS)	All-available to delivery	<u>MBR, NPR, CDR, KUHR, PHC:</u> ICD-10: E282	Inclusion criteria in sensitivity analysis of mothers with polycystic ovary syndrome.
Type 1 diabetes	n/a	<u>MBRN:</u> Checkbox	Defined as perigestational dispensing of insulin and recorded

	All-available to delivery	<u>MBR, NPR, CDR, KUHR, PHC:</u> ICD-10: E10, O240	type 1 diabetes in either MBRN checkbox or as ICD-10 diagnosis code.
	LMP-90 to LMP+97 days	<u>PDR:</u> ATC: A10A (insulin and analogues)	Covariate in sensitivity analysis of mothers with polycystic ovary syndrome.
Type 2 diabetes	n/a	<u>MBRN:</u> Checkbox	Defined as recorded type 2 diabetes in either MBRN checkbox or as ICD-10 diagnosis code.
	All-available to delivery	<u>MBR, NPR, CDR, KUHR, PHC:</u> ICD-10: E11, O241	Only used as inclusion criterion in sensitivity analyses restricted to mothers with a diagnosis of type 2 diabetes, and as exclusion criteria in sensitivity analysis of mothers with polycystic ovary syndrome.
Preexisting diabetes other than type 1 diabetes or type 2 diabetes	All-available to delivery	<u>MBR, NPR, CDR, KUHR, PHC:</u> ICD-10: E12, E13, O242	
Known teratogenic drugs	LMP-90 to LMP+97 days	<u>PDR:</u> ATC: Antineoplastic agents: L01 Isotretinoin: D10BA01, D10AD04, D10AD54 Misoprostol: A02BB01, G02AD06, M01AE56, M01AB55 Systemic retinoids for psoriasis, dermatitis: D05BB, D11AH04 Thalidomide: L04AX02 Valproic acid: N03AG01 Warfarin: B01AA03 Methotrexate: L01BA01, L04AX03	Defined as any of the listed drugs.
Other antidiabetics than metformin or insulin	LMP-90 to LMP+97 days	<u>PDR:</u> ATC: A10B (except A10BA02), A10X	
Chromosomal/genetic anomaly or teratogenic infection (i.e., rubella, cytomegalovirus and toxoplasmosis) in child	Delivery to delivery + ~ 1 year	<u>MBR, NPR, CDR:</u> ICD-10: D821, P350, P351, P371, (Q6190), Q751, Q754, Q87, Q90-Q99 Except Q95 <u>Finnish Register of Congenital Anomalies:</u> ICD-9A: 27911, 75581, 75604, 758, 7598, 7710, 7711, 77121 Except 7584, 75989	Codes in parentheses under ICD-10 are minor anomalies coded according to British Paediatric Association (BPA) modification of ICD that cannot be identified with standard ICD-10. See ESM Table 2 for further details.

ATC = Anatomical Therapeutic Chemical Classification System, CDR = Cause of Death Register in Norway and Sweden, ICD-10 = International Classification of Diseases 10th Revision, KUHR = Norwegian Control and

Payment of Health Reimbursements Database, LMP = last menstrual period, MBR = Medical Birth Register, MBRN = Medical Birth Registry of Norway, NCSP = Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures, NPR = National Patient Register, PDR = Prescribed Drug Register, PHC = Register of Primary Health Care Visits

Supplementary Table 2. Definition of major congenital malformations (MCMs)

Based on EUROCAT (European network of population-based registries for the epidemiological surveillance of congenital anomalies) Guide 1.4, version 01/12/2020.(3)

Subgroup	ICD-10 in MBR, NPR, CDR in Iceland, Norway, Sweden*	ICD-9A in Finnish Register of Congenital Anomalies [†]
1. Nervous system	Q00-Q07 Except (Q0461, Q0780, Q0782)	740-742 Except 74280
2. Eye	Q10-Q15 Except Q101-Q103, Q105, Q135	743 Except 74345, 74361-74363, 74365
3. Ear, face, and neck	Q16-Q18 Except Q170-Q175, Q179, Q180-Q182, Q184-Q187, (Q1880), Q189	744 Except 7441, 74420-74424, 74430, 7444, 74480-74483, 7449
4. Cardiac	Q20-Q26 Except (Q2111), Q246, Q250 and preterm, (Q2541), Q256 and preterm, Q261	745, 746, 7470-7474 Except 74550, 74687, 7470 and preterm 74723, 747325 and preterm, 74741, 74749
5. Respiratory	Q30, Q32-Q34 Except Q301-Q309, Q320, Q322, (Q3300), Q331, Q336	748 Except 7481, 7482-7483 (other), 74840, 74851, 74859, 74862
6. Oro-facial clefts	Q35-Q37 Except Q357, or if occurring with Q00, Q042	749 Except 74908, or if occurring with 740, 74226
7. Digestive system	Q38-Q45, Q790 Except Q381, Q382, (Q3850), Q400, Q401, (Q4021), Q430, (Q4320, Q4381, Q4382), Q444, (Q4583)	750, 751, 7566 Except 75000, 75011-75013, 75024, 75050, 75051, 7506, 75101, 7513, 75166
8. Abdominal wall	Q792, Q793, Q795	75670, 75671, 75679
9. Genital	Q50-Q56 Except Q501 (Q5010, Q5011), Q502, Q505, Q523, Q525, Q527, Q53, Q544, (Q5520, Q5521)	752 Except 75208, 75211, 75243, 75244, 7525, 75261 (urinary), 752621, 75282, 75286
10. Urinary	Q60-Q64, Q794 Except Q610, (Q6190 genetic) Q627, Q633	75261, 753, 75672 Except 75310, 75334, 753485
11. Limb	Q66-Q74 Except Q661-Q669, Q670-Q678, Q680, (Q6810, Q6821) Q683, Q684, Q685, (Q7400)	754-755 Except 7540-7542 (other), 7543, 75440-75443, 75451-75453, 75459, 7546, 7547, 75480-75482, 755525, 755606, 755616, 755645, 755646, 75566, 75581 (genetic)
12. Other	Q27, Q28, Q31, Q75-Q85, Q89 Except Q270, Q314, Q751 (genetic), Q752, Q753, Q754 (genetic), Q760, (Q7643, Q7660, Q7662), Q765, (Q7671), Q790 (digestive), Q792 (abdominal wall), Q793 (abdominal wall), Q794 (urinary), Q795 (abdominal wall), Q825, Q828, Q833, Q845, Q846, (Q8911), Q899	7475-7479, 7482-7483, 7540-7542, 756, 757, 759 Except 7475, 74836, 7540, 7541, 75421, 75604 (genetic), 756085, 75610, 7562, 75630, 75632, 75633, 7566 (digestive), 75670 (abdominal wall), 75671 (abdominal wall), 75672 (urinary), 75679 (abdominal wall), 75686, 7572, 7573, 75751, 75758, 75765, 75902, 75904, 75911, 7598 (genetic), 7599

X. Chromosomal/genetic anomaly or teratogenic infection	D821, P350, P351, P371, (Q6190), Q751, Q754, Q87, Q90-Q99 Except Q95	27911, 75581, 75604, 758, 7598, 7710, 7711, 77121 Except 7584, 75989
Any MCM	Any of the above subgroups (1-12), excluding those in subgroup X	
Multiple MCMs	Follows the 22-step process, outlined in EUROCAT guide 1.4 (Last update version 01/12/2020), section 3.4 (pages 99-104) to remove known sequences	

* Codes in parentheses under ICD-10 (International Classification of Diseases 10th Revision) are minor anomalies coded according to British Paediatric Association (BPA) modification of ICD that cannot be identified with standard ICD-10. For Iceland, Norway, and Sweden, we required at least two diagnosis codes from the same subgroup to be recorded on separate visit dates if the MCM was only diagnosed in outpatient specialist care to increase diagnostic validity. For Iceland, the birthday was assumed to be day 15 of the month of birth since the exact day of birth was not available.

† Finland uses ICD-9A [International Classification of Diseases 9th Revision, A=Atlanta or Metropolitan Atlanta Congenital Defects Program (MACDP) which is almost identical to BPA version], rather than standard ICD-9 for the Finnish Register of Congenital Malformations. For Finland, we only considered validated diagnoses from the Finnish Register of Congenital Malformations.

Supplementary Table 3. Covariate definitions

Covariate	Look-back	Definition	Categories	Notes
Demographics				
Country of delivery	n/a		Finland Iceland Norway Sweden	
Calendar year of delivery	n/a	As recorded in MBR	1996-2000 2001-2005 2006-2010 2011-2015 2016-2018	
Maternal age at delivery	n/a	As recorded in MBR	<25 25-29 30-34 35-39 ≥40	
Parity	n/a	As recorded in MBR	0 1 ≥2	Only for descriptive purposes
Maternal education	n/a	Highest achieved education in year of delivery	Compulsory Pre-university University Missing	Finland: n/a
Relationship status/ cohabitation with partner	n/a	As recorded in MBR	Yes No Missing	
Maternal country of birth	n/a	As recorded in MBR or population register	Nordic Non-Nordic Missing	Finland: defined as Finnish, non-Finnish citizenship
Health factors				
Body Mass Index (BMI) in early pregnancy	n/a	As recorded in MBR, or calculated from maternal weight and height at first antenatal visit (kg/m ²)	Underweight <18.5 Normal 18.5 to <25 Overweight 25 to <30 Obese ≥30 Missing	Finland: partly available since 2004 and from all delivery hospitals since October 2005 Iceland: available since 2012 Norway: available since 2006
Smoking, early pregnancy	n/a	As recorded in MBR	Yes No Missing	Iceland: n/a
Folic acid use before and/or during pregnancy	n/a	<u>MBR:</u> Norway: checkbox Sweden: based on self-reported folate use	Yes No Missing	Finland: n/a Sweden: use before pregnancy n/a

		<u>PDR in Iceland:</u> ATC: B03BB01		
Comorbidities				
Skin infections, incl. candidiasis of vulva and vagina	LMP-365 to LMP+97 days	<u>MBR, NPR, KUHR, PHC:</u> ICD-10: A46, B35-B37, L00-L08 <u>KUHR, PHC:</u> ICPC-2: S09, S10, S74-S76, X72 <u>PDR in Norway (reimbursement):</u> ICD-10: A46, B35-B37, L00-L08 ICPC-2: S09, S10, S74-S76, X72	Yes No	
Diabetic complications	LMP-365 days to delivery	<u>MBR, NPR, CDR, KUHR, PHC:</u> ICD-10: E110-E118, E160, H280, H360, G590, G632, G730, G990, I792, M142, M146, N083 <u>KUHR, PHC:</u> ICPC-2: F83, F92, N94, T87 <u>PDR in Norway (reimbursement):</u> ICD-10: E110-E118, E160, H280, H360, G590, G632, G730, G990, I792, M142, M146, N083 ICPC-2: F83, F92, N94, T87	Yes No	
Chronic hypertension	LMP-365 days to delivery	<u>MBR, NPR, CDR, KUHR, PHC:</u> ICD-10: I10-I15, O10, 011 <u>MBRN:</u> checkbox <u>KUHR, PHC:</u> ICPC-2: K86, K87 <u>PDR in Norway (reimbursement):</u> ICD-10: I10-I15, O10, 011; ICPC-2: K86, K87 <u>PDR in Finland (special reimbursement):</u> 205	Yes No	
Cardiovascular disease	LMP-365 days to delivery	<u>MBR, NPR, CDR, KUHR, PHC:</u>	Yes No	

		ICD-10: I20-I25, I48, I50, I61-I66, I691-I694, I70-I72, I739, I74 <u>KUHR, PHC:</u> ICPC-2: K74-K78 <u>PDR in Norway (reimbursement):</u> ICD-10: I20-I25, I48, I50, I61-I66, I691-I694, I70-I72, I739, I74 ICPC-2: K74-K78		
Epilepsy	LMP-365 days to delivery	<u>MBR, NPR, CDR, KUHR, PHC:</u> ICD-10: G40, G41 <u>MBRN:</u> checkbox <u>KUHR, PHC:</u> ICPC-2: N88 <u>PDR in Norway (reimbursement):</u> ICD-10: G40 ICPC-2: N88 <u>PDR in Finland (special reimbursement):</u> 111, 181, 182, 183, 199	Yes No	
Severe mental illness	LMP-365 days to delivery	<u>MBR, NPR, CDR, KUHR, PHC:</u> ICD-10: F20-F31, F323, F333 <u>KUHR, PHC:</u> ICPC-2: P72, P98 <u>PDR in Norway (reimbursement):</u> ICD-10: F20-F31, F322, F333 ICPC-2: P72, P98	Yes No	
Suspected teratogenic drugs				
Drugs acting on the renin-angiotensin system, including ACE inhibitors, ARBs, renin inhibitors	LMP-90 to LMP+97 days	<u>PDR:</u> ATC: C09	Yes No	
Antithyroid drugs	LMP-90 to LMP+97 days	<u>PDR:</u> ATC: H03B	Yes No	
Immunosuppressive drugs	LMP-90 to LMP+97 days	<u>PDR:</u> ATC: L04AA06, L04AA13, L04AA31	Yes No	

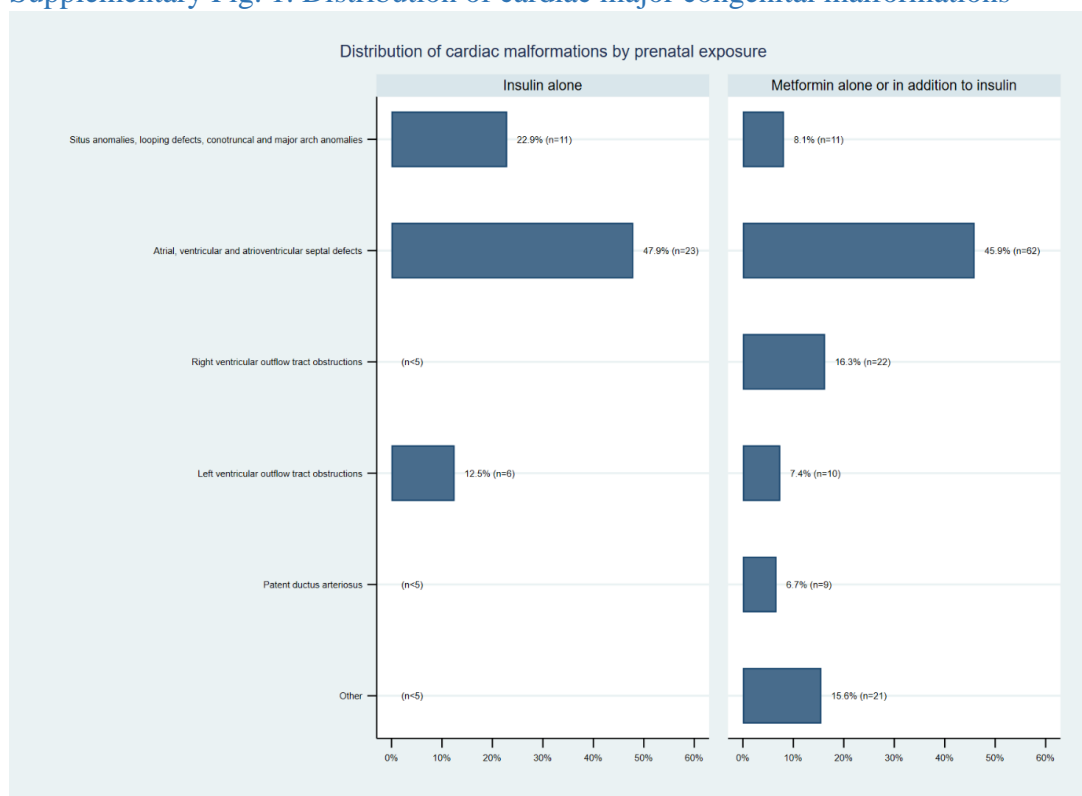
Thalidomide-related drugs	LMP-90 to LMP+97 days	<u>PDR:</u> ATC: L04AX04, L04AX06	Yes No	
Ergot alkaloids	LMP-90 to LMP+97 days	<u>PDR:</u> ATC: N02C	Yes No	
Antiseizure medications	LMP-90 to LMP+97 days	<u>PDR:</u> ATC: N03A excluding N03AG01 (valproic acid)	Yes No	Valproic acid is an exclusion criterion
Lithium	LMP-90 to LMP+97 days	<u>PDR:</u> ATC: N05AN01	Yes No	
Other co-medications				
Other antihypertensives	LMP-90 to LMP+97 days	<u>PDR:</u> ATC: C02, C03, C07, C08, C09	Yes No	
Lipid modifying agents	LMP-90 to LMP+97 days	<u>PDR:</u> ATC: C10	Yes No	
Glucocorticoids	LMP-90 to LMP+97 days	<u>PDR:</u> ATC: H02AB	Yes No	

ATC = Anatomical Therapeutic Chemical Classification System, CDR = Cause of Death Register in Norway and Sweden, ICD-10 = International Classification of Diseases 10th Revision, ICPC-2 = International Classification of Primary Care 2nd Edition, KUHR = Norwegian Control and Payment of Health Reimbursements Database, LMP = last menstrual period, MBR = Medical Birth Register, MBRN = Medical Birth Registry of Norway, NPR = National Patient Register, PHC = Finnish Register of Primary Health Care Visits, PDR = Prescribed Drug Register

Supplementary Table 4. Ethical boards providing approval for data use & approval numbers

Country	Ethical Board	Approval Number
Finland	No Ethical Board approval needed.	THL/1551/6.02.00/2018, THL/1673/5.05.00/2019, Kela 117/522/2019.
Iceland	National Bioethics Committee	VSNb2018060017/03.01
Norway	Regional Committee for Medical Research Ethics South/East Norway	2017/2546/REC South-East
	The Norwegian Data Inspectorate in Norway	17/02068/Norwegian Data Inspectorate
Sweden	Swedish Ethical Review Authority (Etikprövningsmyndigheten)	dnr 2015/1826-31/2, 2017/2238-32, 2018/1790-32, 2018/2211-32

Supplementary Fig. 1. Distribution of cardiac major congenital malformations



Distribution of cardiac major congenital malformations in infants by prenatal exposure to metformin alone or in addition to insulin or to insulin alone.

Supplementary Material References

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