

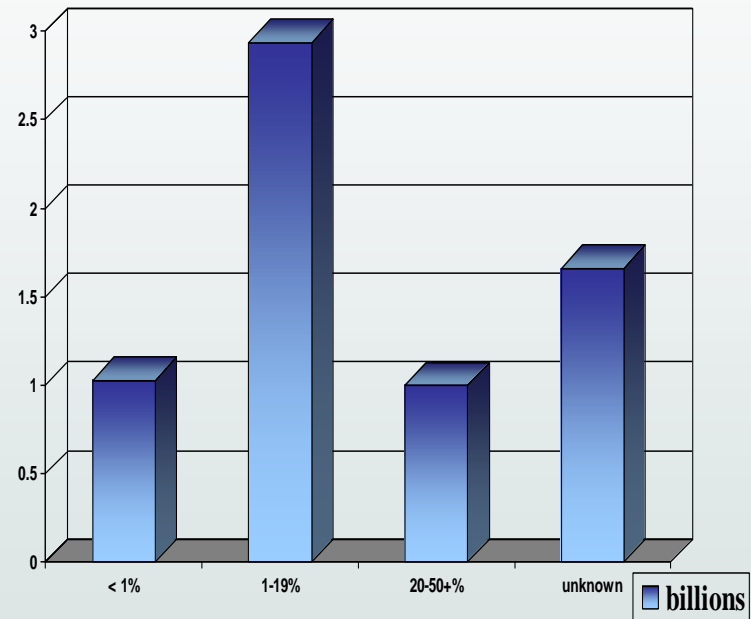
Consanguineous marriages Trends, impact on reproductive health and research priorities

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Training Course in Sexual and Reproductive Health Research
Geneva 2011

Why are we interested in studying consanguinity?

- High consanguinity rates of 20-50% in about one billion of the world population



Global Consanguinity Rates
(Bittles, 2008)

Why are we interested in studying consanguinity?

- Do we really know the adverse effects of consanguinity on health?
- Do we really know if there are advantages versus disadvantages?
- Do we know the evidence-based steps that could minimize any adverse effects of consanguinity in communities?

Why are we interested in studying consanguinity?

- What are the evidence-based guidelines regarding genetic counseling for consanguinity?
- New genetic technologies provide opportunities for research in highly consanguineous populations

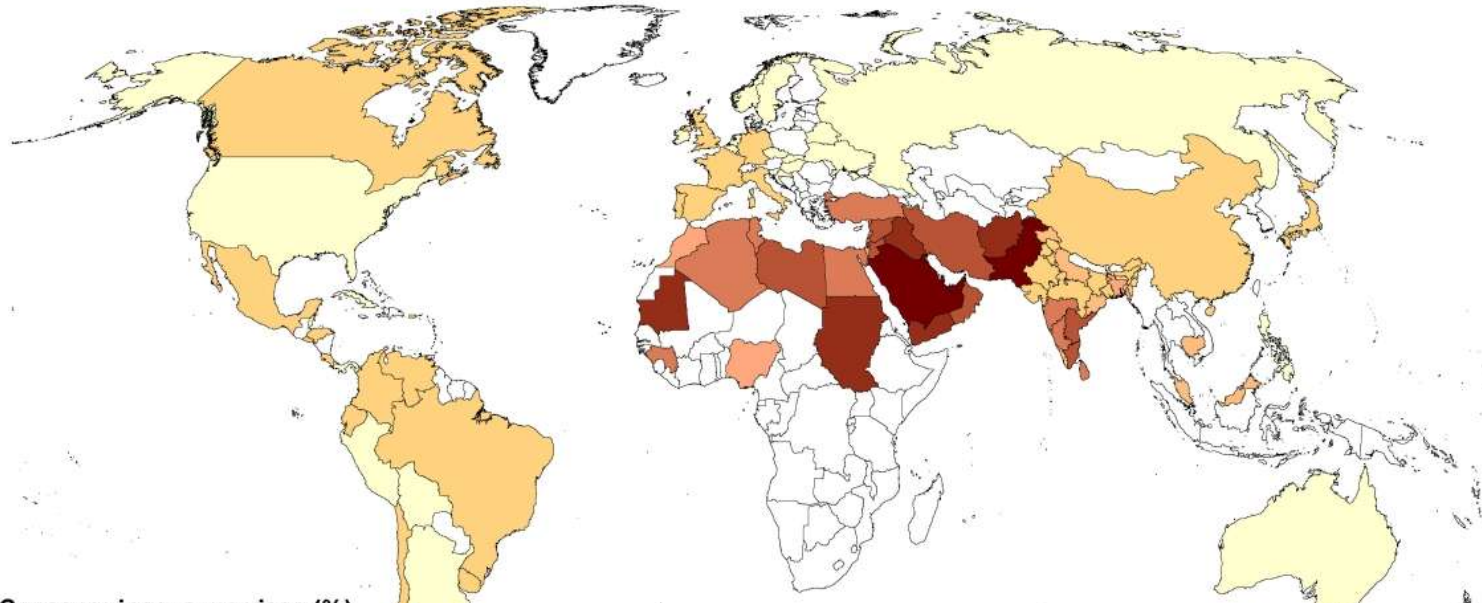
*Global Consanguinity
rates*

Consanguineous marriages

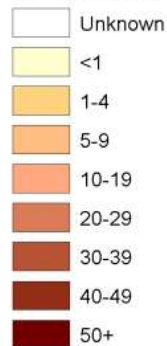
- Consanguineous means related by blood
- As a working definition, unions contracted between persons biologically related as second cousins or closer are categorized as consanguineous, having one or more ancestors in common no more remote than a great-grandparent
- (consag.net; WHO document 1997, EUROCAT)

Global Prevalence of consanguinity

http://www.consang.net/index.php/Global_prevalence



Consanguineous marriage (%)

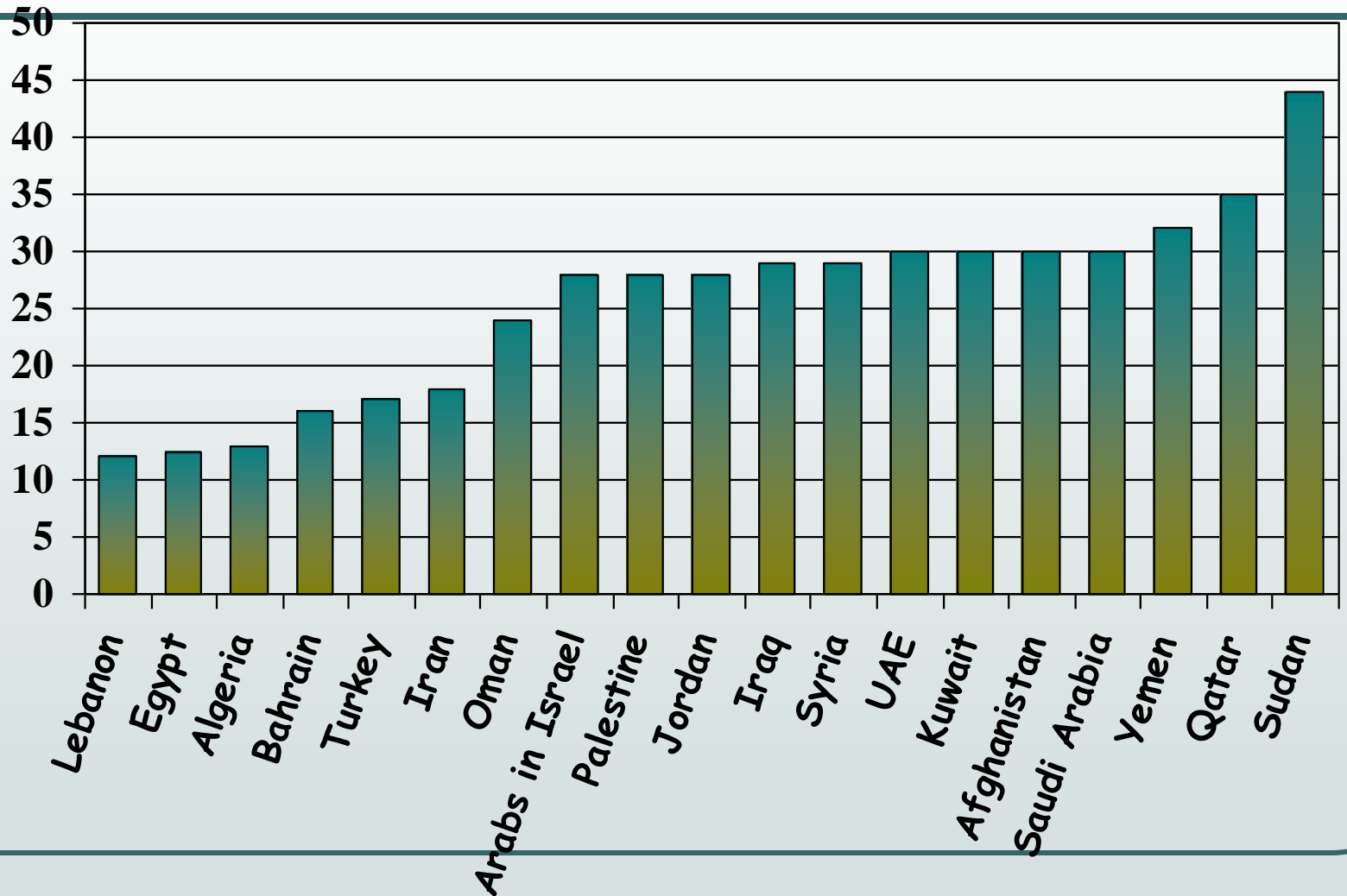


- Less than 1%: United States, Russia, Australia, parts of Latin America and Europe
- 1-10%: China, Latin America, North India, Japan, South Europe and Canada
- 10-50+%: Arab countries, Turkey, Iran, Pakistan, Afghanistan, South India.
- Unknown: Parts of South-East Asia, most Africa

Population types favouring consanguineous marriages

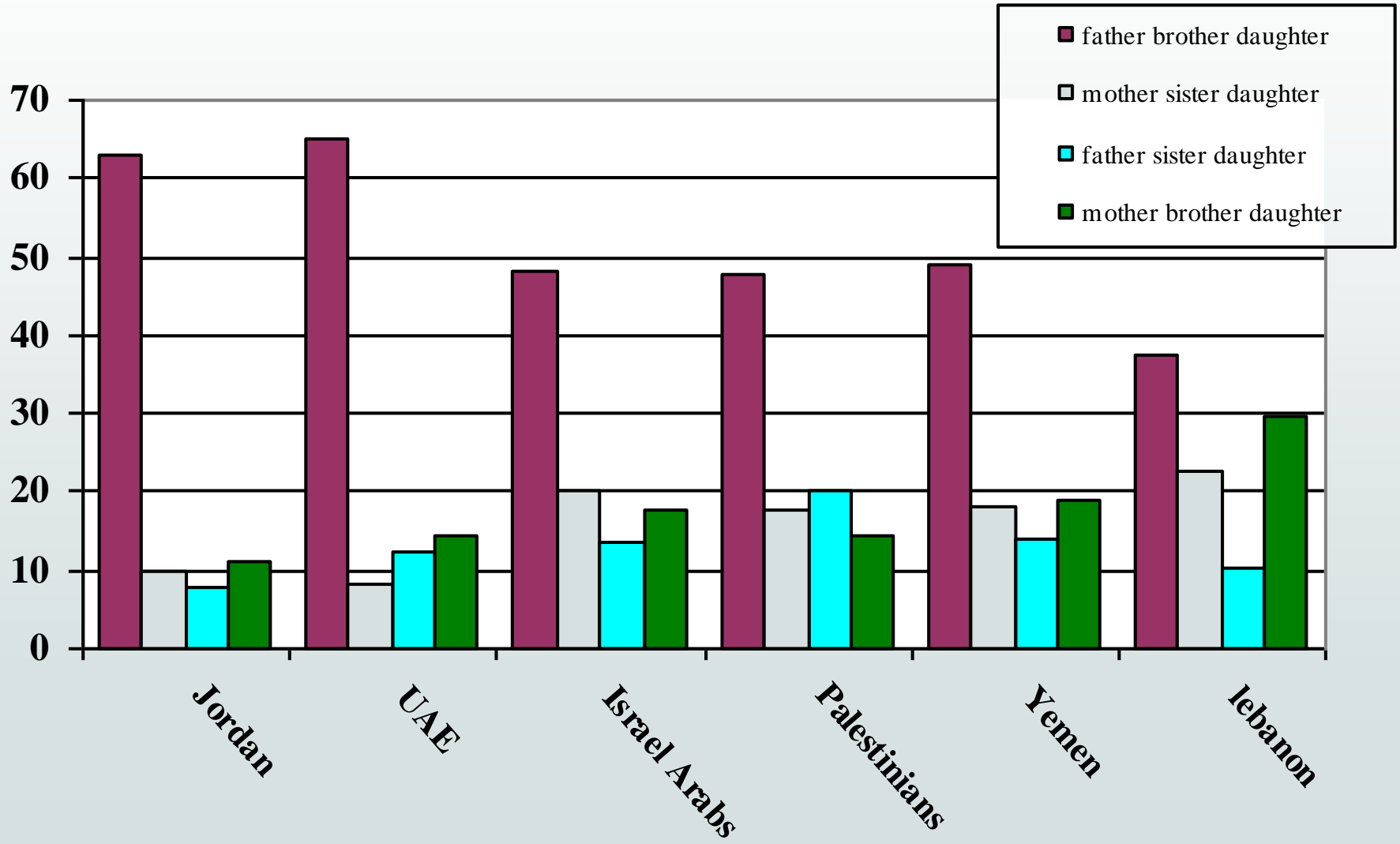
- Major populations in Middle East, North Africa, South Asia (20-50+% of all marriages are consanguineous)
- Major populations in Latin America, Japan, China (1-10% of all marriages are consanguineous)
- Recent migrants from Pakistan, India, the Middle East, North Africa and South Asia, becoming permanent residents in Europe , USA and Canada. (e.g. 2 millions Maghrebians in France, 1.5 million Turks in Germany, 0.5 million Pakistanis in the U.K.)
- Small population isolates where inbreeding is common account for a very small percentage of the world population(e.g. Amish).

Rates of first cousin marriages in highly consanguineous populations (+/- double first cousins)



*Types of first cousin
marriages*

Patterns of first cousin marriage



Reasons for choosing to marry a cousin

- Consanguinity is a deeply rooted cultural trend in certain communities
- More favourable for the women's status. The wife would have better relationship with her in-laws and could be protected by them in time of need.
- There is a general belief that marrying within the family reduces the possibilities of hidden health and financial uncertainties.
- Premarital negotiations regarding financial matters of marriage are more easily conducted, keeping the money and property within the family
- Strengthens family ties, and enforces family solidarity.

Factors affecting consanguinity rates

- Consanguinity rates are higher in rural than urban settings of a certain community
- Higher female education reduces the rate of first cousin marriages
- First cousin marriages are more common when the parents of the couple are consanguineous
- In the same community, consanguinity rates are higher among Muslims than among Christians, for example in Lebanon, Jordan, South India

*Secular trends in
consanguinity rates*

Are consanguinity rates changing with time?

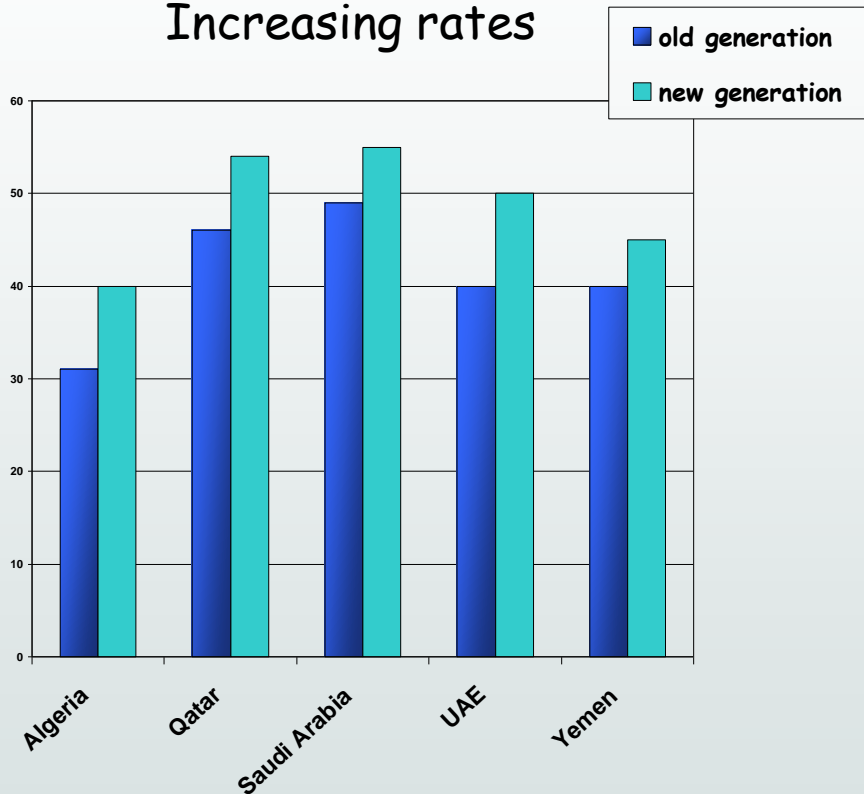
- They have declined in North America and Western Europe. First cousin marriages rate now is around 0.6%.
- They have also declined in Japan: cousin marriages accounted for 5.9-14.7% until 1960's, 5.7% in 1972, and 3.9% in 1983.

Are consanguinity rates changing with time?

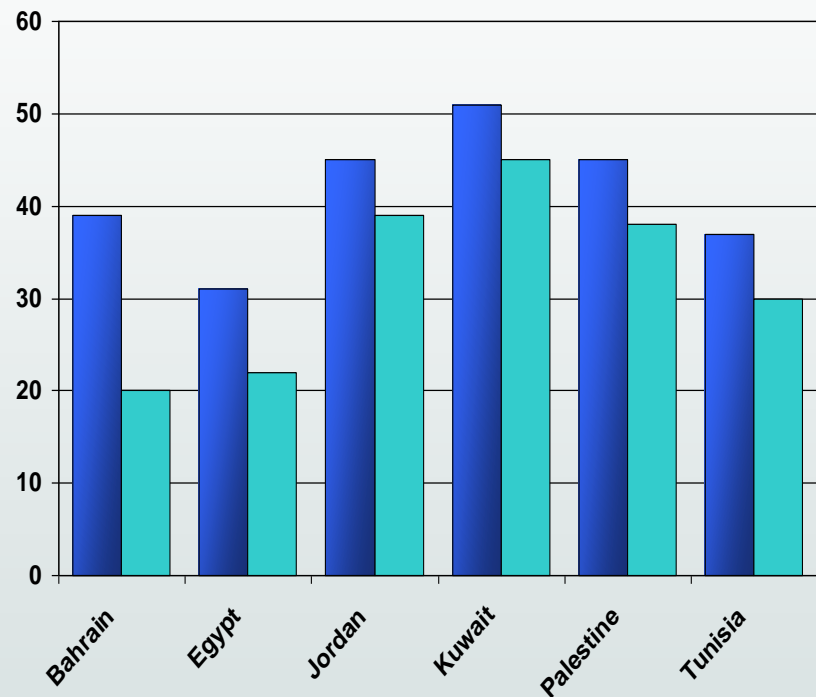
- **Variable secular changes were reported in most countries of North Africa, the Middle East, and South Asia. However, the rate in the present generation in most countries remains at 20-55+%.**

Secular trends in consanguinity rates in highly consanguineous populations

Increasing rates



Decreasing rates



■ Among British Pakistanis the coefficient of inbreeding seems to have increased in a single generation from about 0.024 to 0.0375 ([Darr A](#), [Modell B.](#), 1988)

Why are consanguinity rates not declining in North Africa, West and South Asia?

- Consanguinity is a deeply rooted cultural trend
- It might offer social, psychological and economic advantages
- With improvement in health, there will be more relatives to intermarry.
- The adverse genetic effects on health do not affect 90% of all related marriages.

What factors may decrease consanguinity rate?

- ❖ Higher female education
- ❖ Higher age at marriage
- ❖ Lower fertility
- ❖ More mobility from rural to urban
- ❖ Better economic status of families

Consanguinity and Reproductive Health



Consanguinity and prenatal losses

- ❖ Generally speaking , abortion rates among consanguineous and non-consanguineous couples are comparable
- ❖ Available data suggest that stillborn rates are either similar or slightly higher among consanguineous couples than the non-related couples

Consanguinity and fertility

Most studies have shown similar or higher fertility rates among consanguineous versus non-consanguineous couples.

This may be attributed to:

- younger female age at marriage leading to increased maternal reproductive span.
- compensation for the higher infant mortality among consanguineous couples
- lower prenatal losses among consanguineous couples

Reproductive health parameters in first cousin marriages as opposed to non-consanguineous marriages

- Earlier parental age at marriage
- Younger maternal age at first live-birth
- Fertility rate is slightly higher
- Similar rates of abortion
- Slightly higher rates of stillbirths and infant mortality

Consanguinity and Birth defects

- Generally speaking, frequency of congenital malformations among newborns of first cousin unions is about 2 times the frequency among the general population. *In other words instead of a rate of 2-3% of birth defects in the general population, the risk to first cousin couples is around 4-6%*
- Another estimate puts the offspring of first cousin unions at a 1.7-2.8% increased risk above the population background risk (Bennett et al, 2002).

Consanguinity and specific congenital malformations

- Many studies have shown a positive association between parental consanguinity and congenital heart defects
- The association of consanguinity with cleft lip and palate, and neural tube defects is not clear

Summary of Reproductive Health Parameters among consanguineous versus non- consanguineous couples

- Earlier parental age at marriage
- Younger maternal age at first live-birth
- Higher number of infants born to consanguineous parents
- Lower rates of primary sterility
- Same or lower rates of abortion
- Higher rates of postnatal mortality in offspring
- Higher rates of congenital malformations in offspring
- Higher risk of having offspring with autosomal recessive disorder if present in the family

Consanguinity and Genetic diseases

- No association of consanguinity with
 - autosomal dominant
 - X-linked
 - chromosomal disorders
 - (such as Down syndrome)



- Consanguinity increases the risk of expression of autosomal recessive conditions in the offspring.

This offspring is at a higher risk of being affected by a recessive genetic disease.

Consanguinity and genetic disorders

- Among genetic disorders, only autosomal recessive disorders are strongly associated with consanguinity, approximately 30% of sporadic undiagnosed cases of mental retardation, congenital anomalies and dysmorphism may have an autosomal recessive etiology with risks of recurrence in future pregnancies.
- *Hamamy et al 2007 SMJ*

Consanguinity and genetic disorders

- consanguinity increases the risk of expression of autosomal recessive conditions in the offspring. This effect is more pronounced for rare disorders.

Consanguinity and chronic adult non-communicable diseases (NCD's)

The association of NCD's (such as diabetes, hypertension) with parental consanguinity is still not clear. Controlled studies in populations with high consanguinity rates are needed.

Consanguinity and intelligence

- Severe mental retardation is associated with consanguinity because many autosomal recessive conditions include moderate-severe MR.
- Association of consanguinity with low intelligence is not confirmed

Consanguinity and Genetic Counseling



Proposed steps in counseling a consanguineous couple

- In offering counseling for consanguinity, it is crucial to distinguish between families with a known genetic or inherited disorder and those with no known such disorder by taking a detailed family history and constructing a four generations pedigree (including offspring, siblings, parents, grandparents, aunts, uncles, nieces, nephews, and first cousins)

Premarital and preconception counseling for consanguinity

- There is a genetic disease in the family and the couple are consanguineous
- There is no known genetic disease in the family and the couple are consanguineous

Specific questions addressed to the couple to elicit the presence of a genetic disorder in the family.

Inquire about the presence of any of the following in blood relatives:

- Birth defects or congenital anomalies
- Early hearing impairment
- Early vision impairment
- Mental retardation or learning disability
- Developmental delay or failure to thrive
- Inherited blood disorder
- Unexplained neonatal or infant death in offspring
- Epilepsy
- Undiagnosed severe condition

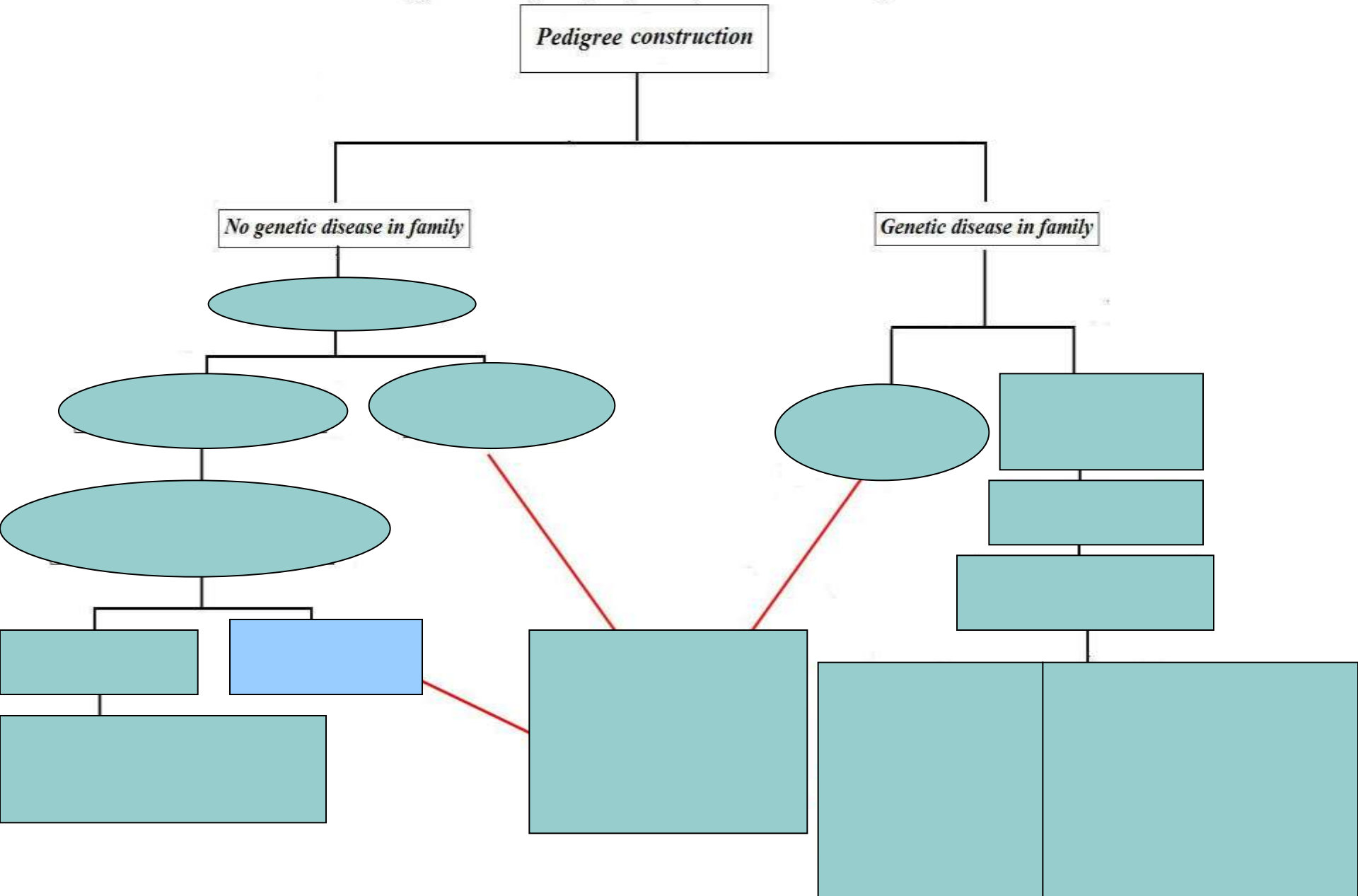
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- In families with hearing, vision or mental disabilities, informative family history coupled by clinical data and investigations could differentiate cases that are associated with consanguinity from cases caused by other factors

If there is no known genetic disorder in the family

- First cousin couples can be given a risk for birth defects in their children of about 4-6%, however studies are still needed to verify this risk figure.
- Risks for other conditions are not established.
- Closer consanguineous relationship such as a double first cousins couple may be given a higher risk for their offspring.

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- Couples who are more distantly related could have a similar risk of birth defects in their offspring as first cousin couples in highly inbred populations. This may be due to the fact that in such inbred populations the actual relationship coefficient among two individuals is much higher than the one calculated based on information given by the couple
 - Among non-inbred general population, the risk to offspring of a couple related more distantly than first cousins could be close to that of a non-related couple

Counseling for consanguinity in primary health care settings



Counseling families with a known autosomal recessive disorder

- Establish Clinical and Molecular diagnosis whenever possible
- Premarital and preconception carrier testing for the consanguineous couple
- If carriers cannot be diagnosed, give risk estimate
- Counseling to minimize further consanguinity unless carriers can be diagnosed
- Counseling couples with affected children by giving reproductive options such as prenatal diagnosis if feasible

Research priorities on consanguinity in populations with high consanguinity rates

Questions that need evidence-based answers include:

Research Questions

- ➔ Will diminishing the consanguinity rates diminish the prevalence of congenital disorders in the community?
- ➔ Will diminishing the consanguinity rates diminish the prevalence of adult non-communicable diseases in the community?
- ➔ Will diminishing the consanguinity rates diminish the infant mortality rate in the community?

Research Questions

- ➔ Will diminishing the consanguinity rates increase the deleterious recessive genes in the gene pool in the future?
- ➔ Will diminishing the consanguinity rates diminish stability and solidarity of the family structure in the community?

Research Questions

- Are consanguinity rates increasing or decreasing? What are the implicated factors?
- What are the advantages and disadvantages of consanguinity that should be known to health care providers and to the population?
- What are the views of society and health care personnel related to consanguineous marriages?
- Are the consanguinity health risks in populations with high rates similar to the calculated risks in western countries with low consanguinity rates?

Research Questions

- What can we tell consanguineous couples requesting premarital and preconception counseling?
- What steps can be advised to minimize the adverse effects of consanguinity on offspring in married consanguineous couples?
- What are the safe, scientific and evidence-based messages that can be delivered through the media regarding consanguinity?

Standardized methodology should be used for all research on consanguinity

- All studies on consanguinity should be standardized
- Accurate definition of the condition for which consanguinity studies are done
- Consanguinity among patients population should be compared to consanguinity in the general population in the same area
- Specify the relationship of consanguinity exactly. Saying consanguineous marriages is not enough

Standardized methodology should be used for all research on consanguinity

- When quoting consanguinity figures, it is important to clarify the number of individuals and how and what were the questions posed to the population studied
- Were confounding factors taken into consideration?
- Inbreeding coefficient is the most accurate determinant of consanguinity in the population studied

Conclusions



Consanguineous marriages remain culturally and socially favored and respected in many countries , mostly in Arab countries, Iran, Pakistan, Turkey and parts of India, as well as in Europe and North America among immigrants from highly consanguineous countries.

Consanguinity and genetic disorders

- Among genetic disorders, mostly autosomal recessive disorders are strongly associated with consanguinity
- Approximately 30% of sporadic undiagnosed cases of mental retardation, congenital anomalies and dysmorphism may have an autosomal recessive etiology with risks of recurrence in future pregnancies. (*Hamamy et al 2007 SMJ*)

Consanguinity counseling in primary health care

- Primary health care providers can counsel for consanguinity provided they possess the recommended education and training
- Education of the public in general and of primary health personnel in particular is an important pillar in clarifying the health and social effects of consanguineous marriages.

Barriers and limitations to counseling on consanguinity

- Minimal knowledge and training of primary health care providers for counseling on consanguinity
- No or limited genetic services and specialists in genetics in some countries

Novel technology and consanguinity

- New technologies including next generation sequencing could eventually help in diagnosing patients affected by conditions known to be genetically heterogeneous. Such technologies could also diagnose if both couple carry the same autosomal recessive gene that causes a severe disorder and thus facilitating counseling on consanguinity.

Research on consanguinity could focus on:

- ✓ Formulating evidence-based practical guidelines for counseling
- ✓ Formulating scientific and feasible Community-based recommendations
- ✓ Deciding research priorities
- ✓ Establishing joint research projects