Pediatric Research Ethics: Islamic Perspectives

Ghiath Alahmad¹* and Kris Dierickx²

¹King Abdullah International Medical Research Center (KAIMRC), King Saud Bin Abdulaziz University for Health Sciences, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Saudi Arabia.
²Centre for Biomedical Ethics and Law, Faculty of Medicine KU Leuven, Kapucijnenvoer, Belgium.

Authors’ contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

ABSTRACT

Background: Children’s participation is crucial in research on childhood diseases and cases associated with childhood health. Despite the existence of many publications that address ethical issues related to the participation of children in clinical research around the world, very little has been written about these ethical issues from an Islamic perspective.

Methods: In this study, we analyzed medical research on children from three Islamic resources: plural fatwas by juristic institutions, the opinions of Islamic medical organizations and individual writings.

Results: Seven plural fatwas from three juristic councils could be found. Only four of them raise ethical concerns about research on children. Two documents from medical organizations were identified.

Conclusion: Three different positions could be concluded from these fatwas: a total prohibition, prohibition unless and permission. Prevention any harm is a major concern in all fatwas. Guardian's consent is necessary, but more details are needed. The guidelines of Islamic Organization of Medical Sciences IOMS reflect the best available Islamic perspective about research on children.
Keywords: Bioethics; children; clinical research; Islam; research ethics.

1. INTRODUCTION

Scientific progress in the fields of biology, medicine, and health relies on research in these areas. Clinical research and medical experiments are important for obtaining better treatments for diseases with the least harmful effects [1].

Many researchers and pharmaceutical companies in the West opt to conduct research in third world countries for economic reasons or because most of these countries do not have strict ethical laws like those in the West [2]. Moreover, many researchers from developing countries conduct research activities in their own countries, including Muslim countries [3]. At the same time, Western scholars have very little knowledge regarding Islamic ethical views on medical issues, including regulations related to medical research, especially on children. Many hear about the Islamic Law, the Sharia, but very few know whether Islamic law on medical issues is compatible with or contradictory to international perspectives on medical research.

Children's participation is crucial in research on childhood diseases and cases associated with childhood health, such as vaccine-related issues, or cases related to drugs designed for children [4]. In the past, many new medications were tested only on adults despite the fact that these medications were applicable to diseases that occur in childhood. This is also true for research on stored tissue material from children, which raises distinct ethical challenges with regard to the involvement of adults [5]. However, children are not simply small adults, and we cannot always apply the results of research conducted on adults to children and young people. This is especially true for the safety of tested medications. Therefore, many research institutions and researchers feel that it is important to conduct research on children [6].

Medical research in Arab countries is increasing rapidly. The high percentage of children in Arab and Islamic societies (compared to Western societies), as statistics show, makes conducting research on children a crucial issue. For example, according to statistics from 2007, 32.5% of the people in Saudi Arabia are 15 years old or younger. (Saudi Export Developing Center, 2007) Medical research on children has made room for ethical debates that reflect the publication of numerous recommendations, ethical laws, and guidelines to achieve a balance between the need for children's participation in medical research and the duty to offer them protection and to avoid doing them harm, as expressed in the Declaration of Helsinki (adopted 1964; latest amendment, 2008) [7] and the International Ethical Guidelines for Biomedical Research Involving Human Subjects (1982; revised, 2002) by Council for International Organizations of Medical Sciences [8].

Key ethical issues addressed by bioethicists regarding clinical research on children include the following: first, researchers can conduct clinical research on children only when it aims to address a pediatric problem or to obtain knowledge related to the health needs of children and cannot be feasibly conducted to the same degree with adults; second, researchers should seek the consent of the parents or legal guardians of children participating in the research; third, researchers should obtain the child's assent according to his ability; and fourth, the researchers should respect the child's desire to withdraw from participation in the research [9].

Religious principles (including Islamic law) form a basis for many practical applications of medical regulations and ethical guidelines [10]. The relationship between Islam and medical research on children has not yet been explored in depth. Despite the remarkable increase in the number of researchers, conducting medical research on children and the existence of many publications that address ethical issues related to the participation of children in clinical research around the world, very little has been written about these ethical issues from an Islamic perspective. This paper will provide a first step in filling this gap. The objective of this essay is to present Islamic opinions regarding medical research on children through an analysis of key Islamic resources on the Islamic attitude toward medical research on children.

2. METHODS

In this study, we analyze medical research on children from three Islamic resources: plural fatwas by juristic institutions, the opinions of Islamic medical organizations, and individual writings.

A fatwa is a legal opinion concerning Islamic law. It is called a plural fatwa if it is issued by a group
in a juristic council and an individual fatwa if it is issued by a single scholar [11]. Plural fatwas play an increasingly important role in representing Islamic views of some issues, especially new matters [12]. We included in our study all Arabic or English, Sunni, plural fatwas that could be accessed online [13]. Our study focused on the Sunni school (87-90% of Muslims are Sunni Muslims and 10-13% are Shia) [14]. We excluded individual fatwas from our resources because there is a problem of selection of scholars. Moreover, after a random pilot survey of approximately 20 websites of scholars from various countries, we could not find any individual fatwas about research on children. Even more survey of medical fatwas mentioned in certain Islamic web used in previous research about organ donation no fatwa related to medical research of children could be found: www.islamonline.net, www.islamweb.net, www.islamicity.com, available www.islam.tc, www.islamtoday.com, and www.understanding-islam.com [15].

In a recent review we showed that 14 juristic councils offer online access to their fatwas: two international councils, the International Islamic Fiqh Academy (IIFA) and the Islamic Fiqh Council (IFC) in the Muslim World League (IFC); four regional councils covering Europe, America, the Gulf and Al-Sham (Syria, Jordan, Lebanon and Palestine); and eight national councils in Saudi, Egypt, India, Malaysia, Singapore, Palestine, Turkey, and Jordan [13]. We surveyed all institutional juristic fatwas released by these institutions.

For the opinions of Islamic medical organizations, we concentrated on the two leading organizations that could be accessed online in either English or Arabic as found in a previous study: the Islamic Organization for Medical Sciences (IOMS) (http://www.islamset.com/ioms/code2004/index.html) and the Islamic Medical Association of North America (IMANA) (www.imana.org) [13]. Although these are not juristic councils, they are medical organizations that adhere to Islamic law.

We excluded fatwas and opinions about embryonic stem cell research, anonymous fatwas and opinions on websites that do not represent official parties.

We continued by exploring related articles on the Islamic perspective on medical research on children. These articles were retrieved using search engines in both Arabic and English and by employing the search terms research+Islam+children. PubMed was used for English articles, and The Comprehensive Encyclopedia (الموسوعة الشاملة) www.islamport.com and The Comprehensive Library (المكتبة الشاملة) http://shamela.ws/ were used to access Arabic resources. We also accessed the King Abdulaziz Public Library in Riyadh, Saudi and the Jarir and Obeikan bookshops.

We attempt to establish a generalized standpoint on research on children from an Islamic perspective. We analyzed the compatibility of this research with international views as stated in official documents, such as the Declaration of Helsinki, Good Clinical Practice GCP and the CIOMS guidelines [7,16,8].

3. RESULTS

3.1 Data Collection

We retrieved nine different documents covering Islamic perspectives on one or more issues about clinical research (Table 1).

We found seven different fatwas from three juristic councils between 1992 and 2008 and two opinions from medical organizations. Six of them have an international scope, and the seventh, by Dar-Alifta Al-Misriyah (Egypt's Fatwa House), [17] has a national scope. Only four of them raise ethical concerns about research on children and three address the subject generally.

Two documents from medical organizations were identified. One of them, by IOMS, has an international scope and includes a separate chapter for research on children [18]. The second, by IMANA, has a North American scope and is not specific to children [19].

The Dar-Alifta Al-Misriyah' fatwa and the IMANA' document addressed stem cells in general [16,18]. They were included because they were not limited to embryos; they also contained a section on research on adults or children.
Table 1. Institutional fatwas about research on children

<table>
<thead>
<tr>
<th>Year</th>
<th>Type of resource</th>
<th>Title</th>
<th>Subject</th>
<th>Author</th>
<th>Background of author</th>
<th>Scope</th>
<th>Size of document</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>Institutional fatwa</td>
<td>Decision 67 about medical treatment</td>
<td>Informed consent No harm Lacking capacity or incompetent</td>
<td>International Islamic Fiqh Academy IIFA</td>
<td>Juristic Council</td>
<td>International</td>
<td>73 lines 1 line</td>
</tr>
<tr>
<td>1997</td>
<td>Institutional fatwa</td>
<td>Decision 94 about cloning</td>
<td>Encourage research Cloning Genetic engineering</td>
<td>International Islamic Fiqh Academy IIFA</td>
<td>Juristic Council</td>
<td>International</td>
<td>105 lines -</td>
</tr>
<tr>
<td>1998</td>
<td>Institutional fatwa</td>
<td>Decision 1/15 about genetic engineering</td>
<td>Genetic research Informed consent</td>
<td>Islamic Fiqh Council IFC</td>
<td>Juristic Council</td>
<td>International</td>
<td>48 lines -</td>
</tr>
<tr>
<td>2002</td>
<td>Institutional fatwa</td>
<td>Decision 3/17 about stem cells</td>
<td>Stem cells research Informed consent Research on children</td>
<td>Islamic Fiqh Council IFC</td>
<td>Juristic Council</td>
<td>International</td>
<td>24 lines 1 line</td>
</tr>
<tr>
<td>2004</td>
<td>Institutional fatwa</td>
<td>Decision 142 about doctor responsibility</td>
<td>Encourage research</td>
<td>IIFA</td>
<td>Juristic Council</td>
<td>International</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>Opinion</td>
<td>International Ethical Guidelines for Biomedical Research Involving Human Subjects - An Islamic Perspective</td>
<td>All research ethics issues presented in CIOMS, including research on children</td>
<td>Islamic Organization for Medical Sciences IOMS</td>
<td>Medical Organization</td>
<td>International</td>
<td>190 pages 2 pages</td>
</tr>
<tr>
<td>Year</td>
<td>Type of Fatwa</td>
<td>Topic</td>
<td>Research Integrity</td>
<td>Authority</td>
<td>Jurisdiction</td>
<td>Lines</td>
<td>Pages</td>
</tr>
<tr>
<td>------</td>
<td>---------------</td>
<td>-------</td>
<td>--------------------</td>
<td>-----------</td>
<td>--------------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>2006</td>
<td>Institutional fatwa</td>
<td>Decision 161 Islamic controls of biomedical research on humans</td>
<td>Research integrity Approving of Islamic perspectives of CIOMS by IOMS Informed consent Protection (even from guardian) of those lacking capacity or incompetent</td>
<td>International Islamic Fiqh Academy IIFA</td>
<td>International</td>
<td>60</td>
<td>4</td>
</tr>
<tr>
<td>2008</td>
<td>Institutional fatwa</td>
<td>Using of stem cells in research (598)</td>
<td>Stem cells research Informed consent Research on children</td>
<td>Dar-Alifta Al-Misriyah</td>
<td>National (Egypt)</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>No date</td>
<td>Opinion</td>
<td>Stem Cell Research: the IMANA perspectives</td>
<td>Genetic research &amp; engineering Stem cells research Conceive to abort the fetus to obtain stem cells</td>
<td>Islamic Medical Association of North America IMANA</td>
<td>Regional (North American)</td>
<td>16</td>
<td>2</td>
</tr>
</tbody>
</table>
Besides these fatwas from councils and opinions of organizations, few individual writings could be found, and none of them could be included in our results because they either presented a Shia point of view [20], merely repeated fatwas and IOMS opinions without farther discussion [21]. Fadel just copied the IOMS opinion in his article about the Islamic perspective of medical research [22], Abu Matar in her master thesis about the ethics of clinical trials talked about the guardians roles and used fatwa 67 of IIFA about preventing research on children especially in case of harm [23].

3.2 Research on Children

Two questions arise from our results: Is it allowed to conduct research on children? And if the answer is yes, what are the allowing requirements? We discussed these two questions in two major themes: the position(s) toward conducting research on children and the requirements of research on children: ethics committee approval, best interest of child, no harm, informed consent of guardians and the assent of the child.

There are three different positions expressed by the studied documents. 1) Research on children is not allowed, as clearly stated by fatwa IIFA 67: “It is not allowed to conduct medical research on people who lack capacity or incompetents, even after guardian approval” [24]. 2) Research on children is not allowed unless there are certain situations, as mentioned by IOMS: first situation, there is an exclusive or preponderant interest or an urgent need of the child in the research, even if the child refuses; second situation, it is absolutely necessary to conduct research on childhood diseases and vaccines and drugs related to children [18]. Fatwa (IIFA 161) accepts IOMS perspectives with regard to children in research [18,25]. 3) Research on children is allowed; this position is taken by fatwa by Islamic Fiqh Council regarding stem cells and by Dar-Alifta Al-Misriyah about using stem cells in scientific experiments (Table 2) [17,26].

Five elements for conducting research on children can be identified in the documents that allow research on children: 1) ethics committee approval was not mentioned in any of the studied fatwas, but it is mentioned in IOMS guidelines [18]. 2) the best interest of the child himself or the group of children [7,8,25] 3) “no harm” is a prerequisite in all documents, even if the harm is only potential harm, as stated in fatwa 161 by International Islamic Fiqh Academy; [25] 4) guardian consent is necessary, but none of the documents provide details on who can be a guardian; 5) child assent is not clearly mentioned in any of the documents; however, IOMS states that the assent of the child cannot replace guardian consent [18].

4. DISCUSSION

4.1 Research on Children

Only few documents about research on children could be found in Islam. This is compatible with our results of a previous study about medical research in general in 13 Muslim countries in the Middle East, that showed that only three countries mentioned research on children in their guidelines [27-30] (See Table 3).

In the fatwas, we notice three different positions regarding clinical research on children: it is not allowed, it is not allowed unless in special situations and it is allowed. At the international levels, the Declaration of Helsinki and the CIOMS guidelines permit research on children under certain conditions [7,8].

The oldest fatwa (IIFA 67, 1992) issued more than 20 years ago, disallows research on children [24]. This prohibition can be explained by a limited awareness about the importance of research on children among the jurists of IIFA, and the lack of a complete and clear understanding of research on children. Moreover, jurists tend to take the safe side that offers better protection of children. This fatwa also reflects the poor participation of medical doctors and specialists in the formulation process of this fatwa [23], since medical doctors are not full members in juristic council but they are just consultants.

Since that fatwa IIFA 67, other fatwas have been issued (IFC 3/17, 2002; IIFA 161, 2006; Dar-Alifta Al-Misriyah 598, 2008) that allow research on children under certain conditions. That will be discussed below [17,25,26].

Islamic Organization Medical Sciences faced a challenge in dealing fatwa (IIFA 67), which disallowed research on children [24]. IOMS agrees to this prohibition, but then it provides two exceptions to allow research on children [18]. These exceptions are: first, the research must be beneficial or address an urgent need for the
Table 2. Ethical concerns in research on children in Islamic resources

<table>
<thead>
<tr>
<th>Document</th>
<th>IIFA 67</th>
<th>IFC 3/17</th>
<th>IOMS</th>
<th>IIFA 161</th>
<th>Dar-Alifta Al-Misriiyah (598)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permission for research on children</td>
<td>No</td>
<td>Yes</td>
<td>No unless</td>
<td>No unless</td>
<td>Yes</td>
</tr>
<tr>
<td>Elements for conducting research on children</td>
<td>Best interest of child</td>
<td>Not applicable</td>
<td>Not available</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Obligation of guardian consent</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>No harm</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Child assent</td>
<td>Not applicable</td>
<td>Not available</td>
<td>Yes</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>Ethics committee</td>
<td>Not available</td>
<td>Not available</td>
<td>Yes</td>
<td>Not available</td>
<td>Not available</td>
</tr>
</tbody>
</table>

Table 3. Children’s research ethics in the guidelines of some Arab Middle Eastern countries

<table>
<thead>
<tr>
<th>Egypt Profession Ethics Regulations</th>
<th>Saudi The law of ethics of research on living creatures</th>
<th>Qatar Guidelines, Regulations and Policies for Research Involving Human Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guardian consent</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Child assent</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Best interest of child</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>No more than minimal risks</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Ethics committee</td>
<td>-</td>
<td>Yes</td>
</tr>
</tbody>
</table>

child; second, there must be a general need for research on childhood diseases, provided that the potential risks are minimal. The different positions between the IOMS opinion and IIFA’s fatwa 67 can be attributed to the difference in the composition of the teams that formulated the documents. In contrast with the IIFA, the IOMS, which was originally an Islamic-oriented medical institution, has a drafting committee composed of scholars in law and medical doctors and experts in medical research, and one of them is not even a Muslim [18].

4.2 Conditions for Research on Children

Looking at the conditions at which the research on children is possible, the following five conditions are mentioned in the international guidelines such as CIOMS guidelines [8]. 1) Ethics committee approval of any research on children must be collected, 2) any research must be in the best interest of child, 3) risk of any research must be not more than minimum risk (do no harm), 4) consent must be collected from the child guardian and 5) if possible the assent of the child should be sought for. In the following, we discuss these five conditions in an Islamic perspective comparing them with international guidelines.

4.2.1 Ethics committee

None of the fatwas refers to ethics committees. Only IOMS talks about the obligation of approval by research ethics committees prior to research on children [18]. The obligation of an ethics committee approval has been mentioned in many international guidelines, such as the Declaration of Helsinki and the CIOMS [7,8], and now is considered one of the most important mechanisms to offer protection to research subjects especially when children are involved.
4.2.2 Best interest of child

Fatwa IIFA 161 and IOMS mention the best interest as one of the conditions for allowing research on children [18,24]. For IOMS the best interest of the child is either the beneficence of the individual child, or the beneficence of childhood community [18]. This implies that therapeutic research, in contrast with IIFA 67 can be interpreted in a broader way: not primary beneficial of the individual child but beneficial to children in the same age [24].

In Islam, even if guardians can decide for the children’s affairs, their decisions must always be in the best interest of the child. It is the parents’ responsibility to provide care and protection for their children. Similarly, many Muslim and Western scholars agree that any decision of the parents must be considered within this framework [31,32]. Taking into account the best interest of the child is the most obvious of respecting the child as a human being [31,33]. The best interest of child is a major concern in research on children and is mentioned in the Declaration of Helsinki and the IOMS opinion [7,18].

4.2.3 Do no harm

The principle "do no harm" is stated by all documents including IOMS guidelines [22].

In Islam and internationally it is accepted that children are a vulnerable group; their protection is the responsibility of their guardians and the community at large [5,34]. The government has the responsibility of controlling this protection through its regulations. This is clearly mentioned in fatwa (IIFA 161), which withdraws parental approval if the research causes harm to the child [25]. This fatwa is consistent with Muslim scholars’ statements that the relationship between parents and children is not just a relationship of mercy and compassion but is also a relationship based on responsibility of parents toward their children, in raising them and offering them better care [35].

Although the documents in this study agree that any medical research to be performed on a child should not cause harm to that child, they do not define or specifically note the harm or its degree or state before it is possible to conduct research with minor risks. Only IOMS specifies that the potential risk should be minimal when conducting research on children [18]. “Minimal risk,” as stated by many authors in the west, is one of the criteria for allowing research on children [36].

4.2.4 Guardian consent

Medical research can be conducted only after obtaining informed consent from the subject, if he is an adult, or from the guardian, if the subject is a child or is unable to give consent. Three fatwas IFC 3/17, IIFA 161 and Dar-Alifta Al-Misriiyah (598) and IOMS require getting guardian informed consent prior any research conducted on children [17,18,25,26]. This prerequisite is also required in the international research ethics guidelines, such as the Declaration of Helsinki and CIOMS guidelines. It is also explicitly mentioned in the writing about ethics of research on children in both documents and individual writings [7,8,37].

Fatwas use word the "guardian", but they do not provide details about who is considered a guardian. The Helsinki Declaration in the context of incompetent subject uses "authorized representative" while the CIOMS speaks about "guardian or parents" [7,8]. The Islamic position regarding who is a guardian, can be deduced from other fatwas or juridical sources such as Al-Mausoха Al-Feqhia (Juridical Encyclopedia) by the Ministry of Awqaf and Islamic Affairs[38]. For Islamic resources generally define the guardian in issues like the child's inheritance, but not for medical research or medical issues. Some authors, such as Shankeeti favor applying the general definition of guardians for medical issues [39]. Consequently, the priority of the guardians of a child according to Islamic resources can be classified as follows: fathers, then grandfathers, and then adult brothers, respectively.

4.2.5 Child assent

Except for the IOMS opinion, child assent in research ethics is not mentioned in any of the documents [22]. None of documents describes from which age on a child can give assent or when it becomes an adult and gives consent. Although not explicitly given a certain age for medical majority, the CIOMS and the Helsinki Declaration mention to the importance of considering child opinion [7,8]. CIOMS stated that from 12-13 year on, the child opinion should be taken into account [7,8].

The age under which children can take decisions related to their health varies from country to country regulations [5]. The ability to take relation
Table 4. Levels of ages according to Al-Mausoha Al-Feqhia

<table>
<thead>
<tr>
<th>Stage</th>
<th>Technique</th>
<th>Child’s Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before the age of distinction</td>
<td>&lt;7 years</td>
<td>Invalid</td>
</tr>
<tr>
<td>Age of distinction (financial issues)</td>
<td>&gt;7 years</td>
<td>Beneficial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neutral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Harmful</td>
</tr>
<tr>
<td>Adult age (financial or criminal issues)</td>
<td>Majority age</td>
<td>Valid</td>
</tr>
<tr>
<td>(defined by government)</td>
<td></td>
<td>Related to other</td>
</tr>
<tr>
<td></td>
<td></td>
<td>party</td>
</tr>
</tbody>
</table>

decisions depends on the degree of capacity, which differs from one child to another and is affected by many factors, such as personal abilities and social context [36,40,41]. A study by Stultiens et al. shows three different types of the between medical majority and legal majority: 1) they are the same, 2) they are different and 3) medical majority must be studied case by case depending on age and maturity [42]. For Islam we can return to the Al-Mausoha Al-Feqhia (Juridical Encyclopedia), which identifies the age of majority in financial and criminal issues, but not in medical issues [38]. It divides ages to three levels. At the first level, a child’s decisions cannot be accepted when he/she is under the age of 7 because he/she cannot understand the nature of the issue. At the second level, from 7 years old to majority, we can only accept those decisions that are both correct and do not cause harm to the child. Decisions by children that are not to be considered correct, and/or cause harm to the child can be rejected by the guardian. The third level is majority (above Table 4). Al-Mausoha Al-Feqhia did not define a specific age for a child to be considered an adult; it referred to the laws of each country [38].

The detailed IOMS document is important and represents the most balanced available document that provides an Islamic perspective on clinical research ethics in general, including research on children. The view provided by IOMS is mostly compatible with international guidelines.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

27. National Committee of Medical & Bioethics (NCMBE). The law of ethics of research on living creatures. Riyadh: King Abdul Aziz City for Science and Technology; 2010.


43. Jordanian civil law. 1976;43.


46. Egyptian civil law. Preliminary / Chapter II. 1948;44.

© 2015 Alahmad and Dierickx; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.